

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION

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MICROBIOLOGY DEVICES PANEL

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MEETING

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GAITHERSBURG, MARYLAND

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FRIDAY,

MARCH 8, 2002

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been edited and FDA  
makes no representation  
regarding its accuracy

The Panel met in the Grand Ballroom,  
Holiday Inn, Two Montgomery Village Avenue,  
Gaithersburg, Maryland, Dr. Michael L. Wilson,  
Chairman, presiding.

VOTING PANEL MEMBERS PRESENT:

DR. MICHAEL L. WILSON, Chairman

DR. KATHLEEN BEAVIS

DR. DONALD A. BERRY

DR. GEORGE G. BIRDSONG

DR. DAVID T. DURACK

DR. JUAN C. FELIX

DR. STEVE GUTMAN

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## VOTING PANEL MEMBERS PRESENT (Continued):

DR. JANINE JANOSKY

DR. LAURA A. KOUTSKY

DR. HERSCHEL W. LAWSON

DR. VALERIE L. NG

DR. KENNETH L. NOLLER

DR. FREDERICK NOLTE

DR. L. BARTH RELLER

STANLEY M. REYNOLDS

## ALSO PRESENT:

JONATHAN S. KAHAN, ESQ.

DR. ELIZABETH R. UNGER

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P-R-O-C-E-E-D-I-N-G-S

(8:36 a.m.)

CHAIRMAN WILSON: I'd like to call the Microbiology Devices Panel to order at this time.

I'd like to begin business with introductions. I'm Dr. Michael Wilson from Denver Health Medical Center, the University of Colorado. I'm the current Panel Chair.

And I'd like to go around the table and have each of the members identify themselves and give their affiliation. We'll begin with you, Valerie.

DR. NG: I'm Valerie Ng, University of California San Francisco

MR. NOLLER: Ken Noller, Tufts University, Boston, Massachusetts.

DR. RELLER: Barth Reller, Duke University Medical Center.

DR. BERRY: Don Berry, biostatistics, University of Texas, M.D. Anderson Cancer Center.

DR. JANOSKY: Janine Janosky, Associate Professor, University of Pittsburgh, School of Medicine.

DR. FELIX: Juan Felix, University of Southern California.

DR. KOUTSKY: Laura Koutsky, University of

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1 Washington, Seattle, Washington.

2 DR. BEAVIS: Kathleen Beavis, Cook County  
3 Hospital.

4 DR. NOLTE: Rick Nolte, Emory University.

5 DR. BIRDSONG: George Birdsong, Grady  
6 Hospital in Atlanta, Georgia.

7 DR. TUAZON: Carmelita Tuazon, George  
8 Washington University Medical Center, Washington, D.C.

9 DR. REYNOLDS: Stan Reynolds, State  
10 Department of Health, Bureau of Laboratories. I'm a  
11 consumer representative.

12 DR. DURACK: David Durack, Becton  
13 Dickinson. I am the industry representative on the  
14 panel.

15 DR. UNGER: Elizabeth Unger, Centers for  
16 Disease Control and Prevention.

17 DR. LAWSON: Herschel Lawson, Centers for  
18 Disease Control and Prevention.

19 DR. GUTMAN: Steve Gutman, Medical  
20 Laboratory Devices, FDA.

21 CHAIRMAN WILSON: Thank you.

22 I'd like to welcome all of the members of  
23 the panel and I appreciate their being willing to  
24 participate today.

25 At this point I'd like to turn the

1 discussion over to Ms. Freddie Poole, who is the  
2 executive secretary.

3 MS. POOLE: Good morning. I'd like to  
4 read the conflict of interest statement.

5 The following announcement addresses  
6 conflict of interest issues associated with this  
7 meeting and is made a part of the record to preclude  
8 even the appearance of impropriety.

9 To determine if any conflict existed, the  
10 agency reviewed the submitted agenda for this meeting  
11 and all financial interests reported by the committee  
12 participants. The conflict of interest statute  
13 prohibits special government employees from  
14 participating in matters that could affect their or  
15 their employees' financial interests.

16 However, the agency has determined that  
17 the participation of certain members and consultants,  
18 the need for whose services outweighs the potential  
19 conflict of interest involved, is in the best interest  
20 of the government.

21 Therefore, a waiver under 18 USC 208(b)(3)  
22 has been granted to Dr. Juan Felix for his unrelated  
23 consulting agreement with a firm that has a financial  
24 interest in the sponsor. He receives less than 10,000  
25 a year. The waiver allows this participant to

1 participate fully in today's deliberations.

2 Copies of this waiver may be obtained by  
3 submitting a written request to the agency's Freedom  
4 of Information Office, Room 12A15 of the Parklawn  
5 Building.

6 We would like to note for the record that  
7 the agency took into consideration certain matters  
8 regarding another panelist, Dr. George Birdsong. He  
9 reported current interests with firms at issue, but in  
10 matters that are not related to today's agenda, the  
11 Agency has determined, therefore, that he may  
12 participate fully in the panel's deliberation.

13 We would like to note that Dr. Elizabeth  
14 Unger, who is a guest discussant at this meeting has  
15 reported her employer's unrelated involvement with a  
16 firm at issue.

17 In the event that the discussions involve  
18 any other products or firms not already on the agenda  
19 for which an FDA participant has a financial interest,  
20 the participant should excuse him or herself from such  
21 involvement and the exclusion will be noted for the  
22 record.

23 With respect to all other participants, we  
24 ask that in the interest of fairness all persons  
25 making statements, all presentations disclose nay

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1 current or previous financial involvement with any  
2 firm whose products they may wish to comment upon.

3 We would also ask as a part of  
4 housekeeping that anyone with cell phones or pagers,  
5 if you could either turn them off or set them on a  
6 silent mode just as a common courtesy for the  
7 speakers.

8 Thank you.

9 CHAIRMAN WILSON: Our new business for  
10 today is a premarket approval supplement for the  
11 Digene high risk HPV DNA. This is a nucleic acid  
12 hybridization in vitro diagnostic device for the  
13 detection of 13 high risk types of human  
14 papillomavirus in cervical specimens. The test as  
15 modified is indicated for use as a general population  
16 screening test in conjunction with the Pap smear for  
17 women 30 years of age and older as an aid to determine  
18 the absence of high grade cervical disease or cancer.

19 We're going to begin with the  
20 manufacturer's presentation. Just as a note to  
21 everyone, FDA has asked that we do finish on time  
22 today because of the number of persons who have travel  
23 arrangements in the late afternoon. So we will be  
24 sticking to the schedule.

25 In the initial presentation for the

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1 manufacturer, there are a larger number of persons who  
2 are presenting. We will be ending that presentation  
3 at 10:15. So out of courtesy to the other persons who  
4 are speaking on behalf of the manufacturer, please  
5 keep in mind that whoever is up at 10:15 will be  
6 stopped and we'll be moving on to the next part of the  
7 program, and we'll do that throughout the day because  
8 we just cannot afford to get behind schedule today.

9 I'd like to ask the panel members to hold  
10 all of their questions until after all nine  
11 presentations are completed, and I'd like to remind  
12 the audience that only members of the panel can ask  
13 questions of the speakers.

14 So at this point we'd like to have the  
15 manufacturer begin their presentation. I believe Mr.  
16 Charles Fleischmann is going to begin.

17 MR. FLEISCHMANN: One clerical note to  
18 begin. I know you have the packet of slides. We have  
19 reordered the slides. There's not new material. Ms.  
20 Poole has a copy of those slides, and we just wanted  
21 to make you aware of it, and if we can facilitate your  
22 understanding or following of the program, that would  
23 be fine.

24 Good morning. I'm Chuck Fleischmann,  
25 President of Digene Corporation.

1 Regulatory and Clinical Affairs has been  
2 one of several major areas for which I have been  
3 responsible at Digene for the last 12 years.

4 In addition, I sit on the board of  
5 directors of ADVAMED, Medical Device and Diagnostic  
6 Trade Association. I chair the ADVAMED board  
7 subcommittee on FDA regulation of in vitro  
8 diagnostics, and frequently represent the diagnostic  
9 industry in discussions with senior FDA and NIH  
10 officials.

11 From that, we have tried to make full  
12 understanding of the highest standards for clinical  
13 and regulatory requirements part of the fabric of our  
14 work at Digene. In the last dozen years, Digene has  
15 worked with the pioneers in the field of cervical  
16 cancer, diagnostics and prevention, particularly  
17 surrounding the unique causal association of human  
18 papillomavirus to the cancer.

19 We have demonstrated the safety and  
20 effectiveness of our device as a follow-up screen for  
21 women with ASCUS PAPs and for use to help rule out  
22 high grade disease following an abnormal PAP.

23 The device is now approved by FDA for  
24 those indications. In the next 75 minutes, you will  
25 hear presentations from scientific, regulatory,

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1 statistical, clinical, and legal professionals with  
2 literally 200 years of experience in molecular  
3 diagnostics in women's health.

4 We believe we can show you that our hybrid  
5 catcher (phonetic) HPV test, when combined with the  
6 PAP as a primary screen for women age 30 and older, is  
7 better clinical medicine than just PAP alone.

8 We are honored to show the weight of  
9 studies from around the world that show the same  
10 thing. Without regard to geography or ethnicity,  
11 Digene's HPV test is better at detecting current  
12 underlying high grade disease than PAP alone. The  
13 combination provides exquisite sensitivity and  
14 extraordinary negative predictive value and,  
15 therefore, makes it possible to better characterize  
16 women at increased or lowered risk of having high  
17 grade cervical disease.

18 We are asking you to review the data and  
19 recommend approval of the combination, not HPV testing  
20 alone; HPV plus PAP for women age 30 and older, a very  
21 specific and conservative indication.

22 This combination takes women's health one  
23 step closer to our goal that no woman should ever die  
24 of cervical cancer.

25 Today's presentation will establish that

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1 HPV causes cervical cancer. The data in the PMA  
2 supplement show HPV testing and cancer's PAP testing.  
3 The combination of cytology with HPV testing is  
4 important for women's health and public health in  
5 general, and that HPV testing can be safely and  
6 effectively incorporated into current clinical  
7 practice.

8 Please ask any questions you have and  
9 thank you in advance for your consideration of our PMA  
10 supplement for expanded product labeling.

11 I will now turn the microphone over to  
12 Mark Del Vecchio, Digene's Director of Clinical and  
13 Regulatory Affairs.

14 MR. DEL VECCHIO: Thank you, Mr.  
15 Fleischmann.

16 Good morning. I'd like to briefly  
17 introduce the speakers Digene has assembled for this  
18 morning's discussion and provide an overview of the  
19 major discussion points.

20 Digene has assembled a distinguished group  
21 of individuals to provide you with an understanding of  
22 the PMA supplement under consideration, including  
23 renowned HPV expert, Dr. Atilla Lorincz, and  
24 epidemiologist, Dr. Xavier Bosch, who will discuss the  
25 causal link between HPV and cervical cancer.

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1 Our statistical team, as you can see, is  
2 comprised of Joe Canner, who performed the primary  
3 data analysis, and Drs. Chiacchierini and Schoenfeld,  
4 who provide statistical support.

5 Dr. Chiacchierini, former head of  
6 biostatistics at CDRH, and Dr. Schoenfeld, professor  
7 in the Department of Biostatistics at Harvard School  
8 of Public Health, will not be presenting, but are  
9 available to answer any of your questions.

10 Contributing to the discussion are three  
11 practicing clinicians and GYN oncologists, Drs. Cox,  
12 Kinney, and Killackey. They will provide a  
13 clinician's perspective of the clinical utility of the  
14 test, use of HPV and PAP for managing women's health.

15 As part of this discussion, an algorithm  
16 describing how HPV fits into the current cervical  
17 cancer screening program will be described. The  
18 information they are presenting this morning will  
19 focus on the technical and practical aspects of HPV  
20 testing and the scientific evidence that supports its  
21 use as a general population screening test  
22 specifically in conjunction with the PAP for women age  
23 30 and older, as Mr. Fleischmann had indicated.

24 In this effort, we will provide a balanced  
25 and reasonable analysis of the underlying clinical

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1 data.

2 As you can see, we have been working very  
3 closely with DCLD over the past two years, and this  
4 effort has resulted in submission of a PMA supplement  
5 under consideration this morning.

6 Digene is seeking to expand its current  
7 and preapproved indication for high risk HPV tests.  
8 Broadly defined, this test is currently approved for  
9 use in qualitative detection of HPV DNA cervical  
10 specimens, the two main intended uses are for ASCUS  
11 screening, for colposcopy referral, and management of  
12 women with low and high grade disease.

13 The proposed intended use expands these  
14 claims to include HPV for general population screening  
15 with a PAP for women 30 and older. This will permit  
16 use of HPV for women with normal PAP, for the further  
17 identification of those at low risk, HPV negative  
18 women, and increased risk, HPV positive women for  
19 underlying high grade disease for cervical cancer.

20 This is possible due to the increased  
21 negative predictive value, the sensitivity of the HPV  
22 test when used as an adjunct to PAP.

23 Now, I would like to introduce Dr. Xavier  
24 Bosch, who will discuss the causal relationship  
25 between HPV and cervical cancer.

1 DR. BOSCH: Thank you, Mr. Chairman.

2 Good morning to everyone. My name is  
3 Xavier Bosch. I'm a cancer epidemiologist. I work at  
4 the International Agency for Research in Cancer for  
5 over ten years, and I've been working in the HPV and  
6 cervical cancer field for about 20 years.

7 I do not have any vested interest in the  
8 company. I sit in their advisory group in Europe, and  
9 my institute, which is a public health institute, has  
10 a research agreement with Digene.

11 The discussion that I'm presenting today  
12 is on causality, which is still extremely relevant  
13 because it sets the ground for any clinical uses that  
14 one claims for HPV testing.

15 I prepared for you a working document that  
16 is in your folders, and now it's in the final stages  
17 for publication. It has been reviewed and acknowledge  
18 by over 28 distinguished scientists worldwide.

19 The review follows the established  
20 criteria of causality that have been used since the  
21 late '50s in assessing the nature of the association  
22 observed between exposure and human cancer, and the  
23 evaluation for the association between HPV and  
24 cervical cancer shows that the compliance with the  
25 major criteria in the majority of the instances.

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1 Follow-up studies that have observed the  
2 transition from normal cytology to high grade lesions  
3 have clearly documented that infection precedes the  
4 advent of disease, and that the disease rate is  
5 substantially affected by the HPV status of the woman  
6 at recruitment.

7 Case control studies have consistently  
8 shown extremely high ratios for what is known in human  
9 cancer. It is extremely consistent geographically.  
10 It is consistent when you break it down by  
11 histological types, if you test once or twice or if  
12 you test for HPV as a group or if you test for high  
13 risk HPV types alone.

14 Molecular studies have also shown that the  
15 transition from normal cell to invasive cancer is  
16 strongly influenced by the presences of the viral DNA.  
17 In fact, the oncogenic proteins of HPV labeled E6 and  
18 E7 are capable of interfering with essential  
19 regulatory genes for cell type and DNA repair, and  
20 that effectively rules away the alternative hypothesis  
21 that HPV might be just a passenger super infection of  
22 the neoplastic tissue.

23 If one had to summarize what is the  
24 current thinking on the etiology of cervical cancer  
25 using the factors that have been established for HPV

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1 positive women and using optimal HPV testing, we've  
2 done that in some 2,300 cases worldwide. And one can  
3 see that perhaps one quarter of them we have HPV alone  
4 as the risk factor. Three quarters of them might have  
5 HPV plus something else, and only a tiny fraction, in  
6 this case less than 400,000, would be linked to a  
7 model that did not include HPV in that scheme.

8 And based on the results, the claim has  
9 been made that HPV is, in fact, a necessary cause of  
10 cervical cancer.

11 So against a background of publications  
12 that show the explosive nature of the field, one can  
13 say that in 1992 and 1995 there were international  
14 review boards certifying HPV certifying HPV 16 and 19  
15 as human carcinogens, Class I, and after that time  
16 there's very little in the literature that even claims  
17 that the central hypothesis of causality has any  
18 alternative.

19 So in conclusion, we can say that HPV is,  
20 indeed, causally related to cervical cancer; that the  
21 DNA of the virus can be recovered from virtually all  
22 cases of cervical cancer worldwide; and that there is  
23 a scientific consensus that HPV is, indeed, a  
24 necessary but not sufficient cause of cervical cancer.

25 In more practical terms, that implies that

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1 the absence of HPV means low risk for disease and the  
2 presence of the vital DNA means an increased risk.

3 And I thank you very much.

4 DR. KINNEY: My name is Walter Kinney.  
5 I'm a gynecologic oncologist. I practice in  
6 Sacramento, California, with the Permanente Medical  
7 Group.

8 My financial associations and those of  
9 Permanente with the Digene Corporation are that ending  
10 approximately five years ago, they provided us with  
11 supplies and laboratory support to conduct a study of  
12 ASCUS triage. Since that time a portion of the public  
13 speaking that I do about cervical cancer screening has  
14 been supported by Digene.

15 I want to speak to you this morning about  
16 the clinical utility of combining cervical cytology  
17 and HPV testing, and I want to start with some  
18 opinions formed in 15 years of clinical practice.

19 The choice of endpoints about trial design  
20 is an important one. Invasive cancer is not an option  
21 as an endpoint for a clinical trial performed in the  
22 United States. Our IRB would not tolerate this, and  
23 no patient would sign the consent after it had been  
24 written by our legal staff.

25 CIN2 and above is a clinically relevant

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1 endpoint because this is the point at which surgical  
2 procedures eventuate from a histologic diagnosis of  
3 this type.

4 One of the requirements of our IRB is the  
5 potential benefit to trial participants. Colposcopy  
6 and biopsy of all or a substantial portion of women  
7 with negative cytology and negative HPV high risk  
8 testing is not viable at the IRB level or at the level  
9 of patient consent, and this opinion of mine is  
10 informed by having spent some years consenting people  
11 for the ASCUS study that I mentioned wherein  
12 colposcopy and biopsy was the single biggest stumbling  
13 block in terms of women's willingness to participate.

14 The potential clinical utility of high  
15 risk HPV testing with cytology is in patients with  
16 negative cytology, which is most of the PAP smears  
17 that we do. For those patients who have negative HPV  
18 tests, there's a measure of reassurance associated  
19 with the knowledge that they don't pair to this virus.

20 And for those patients with positive HPV  
21 tests that are potential benefits with problems that  
22 we have about compliance and about deciding on time to  
23 follow up within the established standards of  
24 practice.

25 And finally, we have a couple of years of

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1 experience with providing hybrid capture II testing to  
2 our physicians for ASCUS triage, and that occurs in a  
3 way such that the physicians are not penalized if they  
4 don't adopt this. They have other options within the  
5 guidelines, and there is nothing bad happens to them  
6 if they don't use this.

7 But the widespread adoption of the testing  
8 in the last couple of years has demonstrated to our  
9 satisfaction the clinical value of the test outweighs  
10 the perceived negatives of having to educate the  
11 patients about the meaning of positivity.

12 Let's move on from opinion to what it is  
13 we know. We know from examining our own failures that  
14 the screening system that produces cervical cancer in  
15 some patients despite easy access to care has two  
16 central problems, one of which is failure to convince  
17 people to be screened in a timely fashion despite  
18 access to care, and the other one is that for  
19 approximately 30 percent of our patients, that single  
20 screen with a dry slide in a three year period prior  
21 to their diagnosis was not sufficient to prevent them  
22 from developing cancer.

23 I would also point out that 95 percent of  
24 our invasive cancer cases occur in people who are  
25 above 30 years of age. So this is the relevant target

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1 population.

2 We've made an effort to figure out the  
3 best way to reach out to people who haven't been  
4 screened in a timely fashion, and we did this large,  
5 prospective, randomized controlled clinical trial with  
6 our own money, and the information that we provide to  
7 patients by mail and by the telephone to convince  
8 them to come in has simply not been adequate up to  
9 this point.

10 Motivating people to comply even in the  
11 absence of financial disincentives has been something  
12 that neither we nor anyone else have figured out how  
13 to do, and there are eight more randomized controlled  
14 trials at this point. This is basically the same  
15 thing.

16 Additional information that we could  
17 provide to patients might conceivably be helpful in  
18 this arena. Certainly we don't do a very good job at  
19 this point.

20 In 1986, a study was published from the  
21 International Agency for Research on cancer pooling,  
22 ten sites outside of the United States, to assess  
23 cervical cancer screening intervals. They defined a  
24 one year interval as zero to 11 months; two years as  
25 12 to 23 months, and so on; and demonstrated that the

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1 protection from cancer as opposed to no screening was  
2 very similar at one, two, and three year intervals.

3 This study cast a very wide shadow in  
4 terms of public health policy and led experts to  
5 conclude that for most women a three year screening  
6 frequency was appropriate.

7 Those conclusions were reflected and are  
8 reflected in the recommendations of a substantial  
9 number of organizations, including the U.S. Preventive  
10 Services Task Force, the American College of  
11 Obstetrics and Gynecology, the American College of  
12 Physicians, and so on.

13 And these recommendations are grounded in  
14 the notion that not everybody needs to be screened at  
15 annual intervals because there are low and high risk  
16 women. The problem is that that risk stratification  
17 has been based up to this point on either historical  
18 factors which don't work well or on the number of  
19 previous negative smears that a woman has had.

20 The clinical consequences of telling a  
21 woman to come back in a year or two years or three  
22 years produce a distribution of intervals to return  
23 for PAP similar to what you see here, and I've  
24 superimposed on this experience of ours the interval  
25 definitions that the International Agency for Research

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1 on Cancer used in their publication.

2 If you tell a patient to come back in a  
3 year, they don't all come back by 11 months. As a  
4 matter of fact, the majority of them don't come back  
5 by 11 months. This compromises the interpretation of  
6 those results.

7 And when we examined this ourselves, we  
8 felt that this was a big enough problem that we  
9 invested a large amount of institutional money in  
10 looking at this on our own with sample size in the  
11 three cells, one, two and three years, about two and  
12 a half times what was available from the pooled ten  
13 site analysis that the IARC did and with what we  
14 consider to be clinically relevant intervals.

15 And the results are that within the  
16 accepted screening intervals of one to three years,  
17 there is a meaningful stratification of risk, and by  
18 three years the risk doubles as opposed to a one year  
19 interval, and that that change is not affected by  
20 whether you've ever had an abnormal PAP smear or  
21 whether you've had two consecutive negative PAPs prior  
22 to the diagnosis of your cancer.

23 My conclusion is that the additional  
24 information that high risk HPV testing as to cytology  
25 is useful to clinicians and patients in multiple ways,

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1 and in the setting where screening intervals of more  
2 than a year are routinely recommended, the presence of  
3 the high risk HPV in women over the age of 30  
4 identifies a group who may benefit from annual  
5 cytologic screening.

6 Thanks for your attention.

7 DR. LORINCZ: Mr. Chairman, members of the  
8 panel, Food and Drug Administration, members of the  
9 audience, good morning. I am Atilla Lorincz, Chief  
10 Scientific Officer and Senior Vice President of Digene  
11 Corporation.

12 I've personally conducted research in the  
13 HPV field for the past 17 years, the last ten years of  
14 which were at Digene Corporation, and I'm the author  
15 or co-author of over 100 peer review publications in  
16 the field.

17 This morning I'm going to describe  
18 clinical study data that Digene is submitting to the  
19 agency in support of our request for a labeling claim  
20 allowing adjunctive use of HPV testing with the  
21 Papanicolaou test in women over the age of 30 years.

22 We reviewed the literature and selected  
23 all relevant and applicable studies. In addition,  
24 several of the studies were designed by Digene in  
25 conjunction with the investigators with the intent of

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1 validating the use of Digene's hybrid capture II HPV  
2 test as a screening adjunct to the PAP test.

3 Digene determined the minimum consistent  
4 requirements for studies to include in our detailed  
5 analyses, and we selected eight studies that met our  
6 criteria.

7 With these data, we wish to demonstrate  
8 the safety and the effectiveness of the hybrid capture  
9 test as a general population screen for cervical  
10 disease for women 30 and over in conjunction with the  
11 PAP.

12 I would like to note that there were not  
13 studies that met our criteria that were excluded.  
14 Some of the key requirements that the studies had to  
15 meet were compliance with Helsinki requirements for  
16 protection of human subjects. Also these had to use  
17 the hybrid capture HPV test, and line data had to be  
18 available for independent analyses, which we conducted  
19 in consultation with our statisticians.

20 These reanalyzed data are the basis of  
21 this presentation. Note our conclusion do not differ  
22 materially from those of the principal investigators  
23 of these studies, several of which have been  
24 published.

25 The size of seven of the eight studies

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1 were statistically meaningful.

2 This is a list of the eight studies that  
3 we selected, along with the names of the principal  
4 investigators and the academic or governmental  
5 institutions involved. As you can see from this list,  
6 there was a substantial number of women enrolled in  
7 these studies, overall totaling more than 44,000,  
8 11,000 of which, or about 25 percent, were from the  
9 USA, with the vast majority coming from the Portland  
10 study, which we regard as one of the key studies of  
11 this presentation.

12 Studies represent a diversity of country  
13 sites and ethnic compositions worldwide. It is our  
14 position that these patients are reflective of the  
15 diverse ethnic groups resident in the U.S.

16 All studies were conducted under a  
17 rigorous pre-written and approved protocols, and  
18 endpoints were carefully determined by expert readers  
19 of cytology and histology. Importantly, in most  
20 studies the histology specimens were reviewed by an  
21 expert pathologist or an expert panel to determine as  
22 accurately as possible the true end condition.

23 Several of the studies have been published  
24 in the peer reviewed literature, as I mentioned, and  
25 the credentials of the principal investigators are of

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1 the highest order, as are the scientific reputations  
2 of the host institutions.

3 I'd like to emphasize that despite  
4 variability of certain protocol parameters, HPV  
5 testing was consistent across studies and the major  
6 conclusions are concordant.

7 Let's review some of the characteristics  
8 of these studies in terms of some of the key  
9 parameters. Six of the eight studies -- I beg your  
10 pardon -- seven out of the eight studies had  
11 sufficient statistical power, and the study from  
12 Hopkins, Baltimore, was included at the request of the  
13 FDA.

14 The majority of studies used the Bethesda  
15 system, and in those -- I beg your pardon.

16 The majority of the studies used the  
17 Bethesda system and histological confirmation was  
18 conducted in all of the studies. Of importance,  
19 masking in the studies was present in every case.

20 This is the description of the target  
21 condition, histologically confirmed high grade  
22 disease. Dr. Kinney has already described the  
23 conditions on the cervix that necessitate treatment.  
24 We used a primary endpoint of CIN2+ as a definition of  
25 high grade disease. In other words, CIN2, CIN3 are

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1       invasive cancer.

2               Additionally, at the request of the FDA,  
3       we reanalyzed the data with a CIN3+ endpoint. That is  
4       excluding the CIN2 category.

5               Next slide.

6               With respect to specimen collection  
7       materials, for the most part the specimen collection  
8       materials used the approved device. Some studies, one  
9       study in particular, the Portland study, used  
10      cervicovaginal lavage and some other studies used a  
11      combination of Cytobrush with or without a spatula.

12              Despite different collection methods, we  
13      observed consistent results. I would like to  
14      emphasize that in the Portland study even with the use  
15      of cervicovaginal lavage, which biased against the HPV  
16      test, we observed a big improvement over PAP alone  
17      after adding the HPV test to the PAP smear.

18              We're going to focus first on the Kaiser  
19      study, which is a large U.S. screening trial of over  
20      10,000 women age 30 and older that were cytologically  
21      normal at baseline. The study had multi-year follow-  
22      up, and the data we present today is based on  
23      evaluation at three years. This study alone supports  
24      the proposed claim that we have before you today.

25              Justification for the three year

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1 determination is under the following assumptions. We  
2 assume that disease detected by repeat PAP smear  
3 screening at three years indicates a very high  
4 probability that disease was present at the outset  
5 because high grade lesions do not regress, and  
6 therefore, we felt it was appropriate to use as a  
7 method of verification repeat PAP smear data on this  
8 group of women conducted over a three year period.

9           Some considerations related to use of the  
10 cervicovaginal lavage specimens are shown here. There  
11 are a number of limitations of this material, such as,  
12 for example, it will collect a large amount of  
13 nonspecific cellular material from the vaginal tract,  
14 not necessarily from the cervix, and thus provides a  
15 less localized specimen which in certain instances may  
16 not detect a small, high grade lesion inside the os.

17           Adjunctive HPV testing using CVL  
18 nevertheless identify the significantly greater number  
19 of women with high grade cervical disease compared to  
20 PAP alone.

21           I'd like to mention that some studies, one  
22 in particular by Hall, et al., compared CVL to brush  
23 and did find a slightly lower sensitivity that was  
24 observed for the CVL.

25           Next slide, please.

1 Well, this talks about the applicability  
2 of foreign studies to the U.S. population. The PAP  
3 was read by expert pathologists in three studies, and  
4 the PAP methods and the Bethesda system was used in  
5 six of the studies.

6 The resident improvement in sensitivity of  
7 the HPV test over the PAP is applicable to the U.S.  
8 over a spectrum of disease prevalence.

9 These PMAs represent independent  
10 prospective analyses. Six of these had sufficient  
11 statistical power to stand on their own as a disease  
12 endpoint, and the seventh study, which was conducted  
13 in China, showed no evidence of verification bias.  
14 I'd like to emphasize that such a study could not be  
15 done in the U.S. for the reasons mentioned by Dr.  
16 Walter Kinney with respect to IRB concerns or  
17 compliance of the patients.

18 Nevertheless, in China all of the women  
19 were biopsied, and apparently there was minimal or no  
20 verification bias detected due to no disease being  
21 found in the PAP-HPV negative women.

22 And the eighth study provided additional  
23 support in U.S. data.

24 Next slide, please.

25 I'd like to just go into the data here,

1 and we're going to use the CIN3 as our principal  
2 endpoint for these particular set of tables. I'd like  
3 to mention the Portland study which had a CIN3+  
4 endpoint. CIN2 was not done in Portland as an  
5 endpoint.

6 We look at the numbers of patients here,  
7 and we looked at the prevalence of CIN3. It varied  
8 from a low in Baltimore, Johns Hopkins' study, or  
9 Germany of about .2 to .4 percent up to as high as  
10 four percent in South Africa.

11 I'd like to emphasize that the prevalence  
12 of disease in the U.S. in the Portland study and in  
13 the Johns Hopkins study was at the lower end  
14 consistent with other international studies, such as  
15 from U.K. and Germany.

16 I'd like to spend a little bit of time on  
17 this particular graph showing the sensitivity of the  
18 HPV test combined with PAP, compared to PAP alone.  
19 When we look at these studies, we see a dramatic  
20 improvement in the sensitivity of the HPV combination  
21 with PAP relative to the original PAP test alone.

22 For example, in the Portland study going  
23 from 50 to 80 percent. The same thing was observed in  
24 several of the other studies.

25 Of note, in those studies where the PAP

1 smear had a relatively low sensitivity, 50 to 60  
2 percent, such as in Germany, Mexico, Portland,  
3 Baltimore, Johns Hopkins study, the addition of the  
4 HPV test led to an important and dramatic increase in  
5 the sensitivity of the combined tests, and this  
6 increase was far greater than would have been expected  
7 by chance alone. So we feel that that shows a very  
8 important improvement in the combination of the test.

9 And this chart here demonstrates the  
10 statistical analyses of the confidence intervals  
11 around those estimates. In six out of the eight  
12 studies here we met or exceeded the criteria that was  
13 agreed to in discussions with the FDA. As we can see  
14 in several of the studies, the mean value of the  
15 sensitivity improvement was 100 percent.

16 In two of the studies the lower end of the  
17 bound of the 95 percent confidence interval due to  
18 power issues was below the 25 percent level, but in  
19 six of them it was significantly above that level.

20 Next slide.

21 Looking at the specificity of the  
22 combinations, either PAP alone or PAP plus HPV  
23 combined for CIN3, we see a small decrease in  
24 specificity of the combined test relative to PAP alone  
25 as would be expected by adding the two tests like

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1 this.

2 We believe that the data demonstrate that  
3 the decrease in specificity is minor. As shown here,  
4 assessing the decrease in specificity of the combined  
5 tests relative to the predetermined cutoff that had  
6 been agreed to, which is a specificity decrease of  
7 less than or equal to ten percent was acceptable.  
8 Seven of the eight studies met those criteria, and  
9 only one, South Africa, did not meet those particular  
10 set of criteria.

11 Next slide.

12 Looking at the negative predictive value,  
13 I'd like to emphasize that we have expanded the range  
14 on the Y axis. It's 99 to 100 percent. This is by  
15 way of emphasis of the differences in negative  
16 predictive values since negative predictive values in  
17 rare diseases tend to not differ very much, but those  
18 differences are extremely important.

19 We can see that in all studies, again, as  
20 observed with the sensitivity, the combined negative  
21 predictive value of a HPV adjunct to the PAP was  
22 higher than the PAP alone.

23 Next slide.

24 Looking at the positive predictive values,  
25 despite the variations in prevalence in different

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1 parts of the world, despite the different ethnic  
2 composition of the studies, we see that the positive  
3 predictive values of the PAP alone or PAP plus HPV  
4 were very similar in the majority of these studies  
5 beyond the order of perhaps eight to 20 percent, in  
6 that range for either PAP or HPV plus PAP.

7 Now, I'd like to focus on the main  
8 endpoint that Digene has presented, which is the CIN2+  
9 endpoint, including this neoplastic category that is  
10 slightly lower, CIN2, combined with CIN2-3. The value  
11 of these data are that there are greater numbers of  
12 women with CIN2+, the combined prevalence of all of  
13 these conditions now being on the order of half  
14 percent to up as high as six percent.

15 As I mentioned before, the Portland data  
16 are missing from here because they only had a CIN3+  
17 endpoint, and in keeping with our conclusions from the  
18 CIN3 endpoint, the sensitivity of the HPV combination  
19 with PAP was always higher than the sensitivity of PAP  
20 alone, substantially higher in most studies, and the  
21 specificity decrease was quite small.

22 I would like to show two slides.

23 Next slide.

24 This shows the assessment of the  
25 sensitivity improvement of PAP and the combination of

1 PAP plus HPV against the 24 percent relative  
2 sensitivity improvement. Seven of the eight studies  
3 met those criteria. The Johns Hopkins study actually  
4 had a mean value of 100 percent, but because of its  
5 small size, the lower bound did not cross the 25  
6 percent threshold.

7 Looking at the specificity decrease  
8 relative to PAP, seven of the eight studies met or  
9 exceeded by quite a substantial amount the criteria.  
10 The South African study did not meet the criteria,  
11 this particular case with the 95 percent being below  
12 ten percent.

13 Next slide.

14 So some of the potential limitations of  
15 the studies are Portland used the CVL, which is not a  
16 currently approved device for HPV. Some other studies  
17 used either plastic spatula and Cytobrush or Cytobrush  
18 alone.

19 I've already alluded to the fact that we  
20 believe that cervicovaginal lavage is sufficient for  
21 HPV detection, and although it biases against  
22 detection of high grade disease, it still yielded  
23 important adjunct of sensitivity.

24 The Cytobrush spatula -- sorry to jump  
25 ahead -- the Cytobrush spatula combination is approved

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1 for the PAP. In our preliminary studies, we  
2 demonstrate -- we have demonstrated equivalence for  
3 HPV DNA detection, and this data has not yet been  
4 submitted to the agency, but it's in preparation to  
5 show.

6 And this particular study looks at the  
7 brush spatula versus CVL. This table is actually from  
8 the study of Hall, et al. If you'll remember back a  
9 few slides, it demonstrates clearly that for detection  
10 of high grade disease, HPV positivity by brush was  
11 improved relative to CVL and for low grade disease  
12 brush appear to be somewhat better, whereas for  
13 detection of HPV in PAP negative women there did not  
14 appear to be that much of a difference.

15 So we believe that these data demonstrate  
16 that the brush is an improved device relative to CVL.

17 In the conclusions for all of these  
18 presentations then, I'd like to emphasize a number of  
19 important points. These eight studies represent  
20 multiple independent sites and multiple independent  
21 studies done at different institutions by different  
22 investigators comprising 44,000 women, over 44,000  
23 women with 25 percent coming from the U.S.

24 There is a broad ethnic representation,  
25 and these ethnic groups are currently resident in the

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1 U.S.

2 A broad range of prevalence. Our data, I  
3 believe, show that irrespective of the range of  
4 prevalence observed, the performance of the test  
5 certainly did not change. Sensitivity was not  
6 affected or would not expect to be affected based upon  
7 statistical considerations.

8 Most of these were designed to maximize  
9 the sensitivity of the PAP smear. By that I mean that  
10 expert panels or expert cytopathologists spend  
11 considerable time insuring that the PAP smear was  
12 performed to the highest level.

13 This did not happen in all studies, but it  
14 did happen in most, and because the PAP is a test that  
15 is subject to expert review, it is our position that  
16 the performance of PAP smear alone in these studies  
17 is, for the most part, considerably better than would  
18 be found in a routine screening setting.

19 That conclusion is not the same for a test  
20 such as HPV, which uses an objective endpoint that is  
21 generated by a machine and a computer analytical  
22 algorithm.

23 Seven of the eight -- despite the  
24 variability of certain protocol parameters, HPV was  
25 consistent across the studies, and the major

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1 conclusions were concordant. Seven of the eight  
2 studies were statistically significant.

3 And finally, in conclusion, in all studies  
4 HPV is an adjunct of the PAP, is a more sensitive  
5 indicator for cervical disease than PAP alone, with  
6 only a minor reduction in specificity of the combined  
7 tests.

8 Thank you very much for your attention.

9 MR. CANNER: Good morning. My name is  
10 Joseph Canner, biostatistician and regulatory  
11 consultant at Hogan & Hartson in Washington, D.C.

12 I have no financial interest in Digene.  
13 I'm being paid by Digene for my time and  
14 transportation costs.

15 I was primarily responsible for the  
16 statistical analysis of the data from the eight  
17 studies that Dr. Lorincz described, and I am joined  
18 here, as was mentioned earlier, by Dr. Richard  
19 Chiacchierini from C.O. McIntosh and Dr. David  
20 Schoenfeld in the Harvard School of Public Health  
21 behind me.

22 During the time period that Digene was  
23 identifying and obtaining data sets from the various  
24 investigators, we were also preparing a prospective  
25 statistical analysis plan. This plan was developed

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1 prior to any data analysis and was discussed with FDA  
2 on several occasions.

3 Now, before we get into the specifics of  
4 the analysis plan, there are two important points to  
5 note, some of which I mentioned earlier.

6 Since each study was conducted  
7 independently under a different protocol, the decision  
8 was made to analyze these studies separately. Six of  
9 these studies had sufficient sample size for the  
10 outcomes of interest, and so we felt comfortable with  
11 this approach

12 The two smallest studies were included for  
13 confirmative purposes, China because of a complete  
14 biopsy verification and Baltimore because it is a U.S.  
15 population conducted by a reputable institution,  
16 namely, Johns Hopkins.

17 Second, the success criteria for each  
18 study were developed based on two assumptions:

19 Number one, that the outcome of interest  
20 for cervical disease were CIN2 or higher;

21 And, secondly, that the success criteria  
22 be applied to the estimates of sensitivity and  
23 specificity uncorrected for verification bias.

24 The first assumption is important because  
25 the December 2000 panel indicated its preference for

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1 CIN3 or above, which FDA agreed with. Accordingly,  
2 Digene has included analyses based both on CIN2 and  
3 above and CIN3 and above.

4 However, the sample size of positive cases  
5 drops considerably for CIN3 and above, resulting in  
6 wider confidence intervals.

7 The second assumption about verification  
8 bias is important because different approaches to  
9 verification bias can result in drastically different  
10 conclusion, as I'll discuss later.

11 Several statistical analyses related to  
12 sensitivity were outlined in the statistical analysis  
13 plan. The McNemar test was mentioned. It's a  
14 standard test for data in which each patient is tested  
15 with two different diagnostic methods.

16 However, this test is primarily of use in  
17 comparing PAP alone with HPV alone, which is not the  
18 focus of today's presentation.

19 Several measures of clinical significance  
20 are defined in the statistical analysis plan. The one  
21 we are focusing on today is a relative increase in  
22 sensitivity of the combined test over PAP alone.

23 This is also referred to by the FDA  
24 statistician as a decrease in false negative rate, or  
25 FNR, and is calculated as the absolute difference in

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1 sensitivity, which is the combined test sensitivity  
2 minus the PAP sensitivity, divided by one minus the  
3 PAP sensitivity.

4 This can also be thought of as the  
5 sensitivity of HPV when the PAP is negative.

6 This measure was preferred over the  
7 absolute difference in sensitivity due to the wide  
8 variation in PAP sensitivities in these studies, and  
9 since the interpretation of absolute sensitivity  
10 depends on the PAP sensitivity.

11 For example, a five percent absolute  
12 difference is interpreted much differently if the PAP  
13 sensitivity is 90 percent than when the PAP  
14 sensitivity is 60 percent.

15 In contrast, the relative increase in  
16 sensitivity provides a more intuitive assessment of  
17 improvement that is less dependent on PAP sensitivity.  
18 And I give a couple of examples here, that an increase  
19 from 90 to 95 percent yields a relative improvement of  
20 50 percent, as does an increase from 60 to 80 percent.

21 The success criteria for this endpoint was  
22 set at 25 percent, and although it was not explicitly  
23 mentioned in the protocol how this success criteria  
24 would be evaluated, it is widely assumed that the most  
25 appropriate method is to calculate a lower 95 percent

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1 confidence bound.

2 The FDA reviewer used Booscott (phonetic)  
3 methods to calculate this confidence bound. We  
4 calculated the bound using well accepted exact  
5 binomial methods which give very similar results.

6 For specificity, the method is simply to  
7 compute the absolute difference between PAP and the  
8 combined test and calculate the lower 95 percent  
9 confidence bound.

10 The success criteria was set at a  
11 difference of no more than ten percent, and the  
12 statistical analysis quite clearly indicates that this  
13 criteria was to be evaluated using the confidence  
14 bound.

15 You've seen these graphs before, but just  
16 to remind you in case it wasn't obvious before how  
17 this was defined, sensitivity results for CIN2 and  
18 above show that the primary outcome was met for six  
19 out of the seven studies. Portland is not included in  
20 this graph because only CIN3 and above was evaluated  
21 in that study.

22 In the remaining study that did not exceed  
23 the 25 percent bound, the adjunctive sensitivity was  
24 100 percent, and a relative increase in sensitivity is  
25 also 100 percent, and the lower confidence bound

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1 nearly met the 25 percent criteria.

2           Sensitivity results for CIN3, despite the  
3 reduced power mentioned earlier shows similar results.  
4 The success criteria was met in six out of the eight  
5 studies. In the remaining two studies, the adjunctive  
6 sensitivity was 100 percent, and the relative increase  
7 in sensitivity was also 100 percent, indicating that  
8 all cases of cervical disease missed by PAP were  
9 identified by HPV.

10           Thus, the test reached the maximum  
11 possible performance level, but because of the small  
12 sample size, the confidence bounds extend below 25  
13 percent.

14           It's also worth reemphasizing the striking  
15 consistency between these results. Although we have  
16 chosen not to perform a combined analysis at this  
17 time, there is no statistical reason why this could  
18 not be done, and it is clear from this picture what  
19 the overall increase in sensitivity would be, and  
20 clearly the confidence bound would be significantly  
21 higher than 25 percent.

22           Specificity results, again, for CIN2 and  
23 CIN3 are very similar and show that seven out of eight  
24 studies met the success criteria and that South Africa  
25 exceeded the bound by a small amount.

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1                   We've heard a lot today about verification  
2 bias, also known as ascertainment bias or referral  
3 bias. So what is verification bias?

4                   In most studies of cervical disease only  
5 a select group of patients are referred for  
6 colposcopy, that is, those that have some indication  
7 of disease, whether it be PAP positivity, HPV  
8 positivity, visual inspection, and so on.

9                   this results in a large group of patients  
10 who are negative on all of the diagnostic criteria and  
11 for whom there is no colposcopic or histologic  
12 confirmation of their negative status. And I've given  
13 an example, theoretical example here. You can see the  
14 cells D and H which represent those situations where  
15 the PAP is negative and the HPV is negative. Those  
16 cells do not have confirmation of disease, and so  
17 there's uncertainty about whether these double  
18 negative women are truly negative, that is, should  
19 they be in the H cell or whether some may be positive  
20 and belong in the D cell.

21                   In cervical disease, this bias is  
22 generally considered to be small, but any  
23 misclassification of patients as negative when  
24 they're, in fact, really positive, that is, putting  
25 them in H when they really belong in D, results in an

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1 over estimate of sensitivity and an under estimate of  
2 specificity.

3 Many different valid approaches can be  
4 taken to deal with verification bias. First of all,  
5 in some studies there are no patients available for  
6 verification bias, although none in this series of  
7 eight studies. In other words, such studies, there  
8 may be no double negative patients referred to  
9 colposcopy or biopsy.

10 There are several statistical methods that  
11 can be used in this situation, but this is not an  
12 ideal situation, and in particular, those methods may  
13 not be appropriate in the evaluation of a combined  
14 test.

15 The second approach is to do no  
16 adjustment, and this is a common approach primarily  
17 because it does not require additional assumptions and  
18 computations, and for certain outcome measures, such  
19 as, for example, the ratio of sensitivities or the  
20 number of cases of disease identified by HPV,  
21 verification bias, in fact, has no impact and can be  
22 ignored.

23 This is because verification bias refers  
24 to cases that were missed by both PAP and HPV, and so  
25 adjustment for verification bias simply reduces the

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1 sensitivities of both in parallel, leaving their  
2 rankings unchanged.

3 If you think back to the bar graphs that  
4 Dr. Lorincz showed, even if you shrink both of the  
5 bars by the same factor, the substantial differences  
6 between them still remain.

7 There are several possible methods for  
8 adjustment, but this can only be done if there are  
9 some double negative patients that were referred to  
10 colposcopy, and the proportion of patients who turn  
11 out to be positive can then be used to extrapolate to  
12 the entire population of double negative patients and  
13 determine how many should be reassigned as positive.

14 There are generally two ways in which this  
15 can be done. First, a random sample, where a small  
16 proportion of double negative women chosen at random  
17 are asked to return for colposcopy, while a truly  
18 random sample provides the most statistically valid  
19 method of adjustment, there are typically compliance  
20 problems with the random sample, which can bias the  
21 adjustment.

22 In addition, there is still considerable  
23 uncertainty about the appropriate adjustment factor  
24 since there is variability associated with the  
25 estimate. In other words, even if no disease is found

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1 in that sample, can we really be sure that the rate is  
2 zero?

3 A second alternative is using directed  
4 colposcopy. In many studies patients are referred to  
5 colposcopy for reasons other than PAP and HPV. This  
6 sample can also be used to adjust for verification  
7 bias. However, this is clearly less useful than the  
8 random sample since these patients are at higher risk  
9 of disease than the double negative population as a  
10 whole.

11 And finally, an alternative is to send all  
12 women to colposcopy and biopsy. This is not  
13 considered to be an ethical alternative in most  
14 Western countries, and patients are unlikely to agree  
15 to participate in such a study in any case.

16 So, in summary, there are a variety of  
17 methods for dealing with verification bias. None of  
18 them is entirely ideal, and it is our view that this  
19 issue must be approached with caution.

20 This slide summarizes the referral  
21 criteria for each of the studies in which a subset of  
22 negative patients were referred to colposcopy. In  
23 Germany, the U.K., and Costa Rica, a random sample of  
24 double negative patients were referred for colposcopy,  
25 and in Mexico, South Africa, and Johns Hopkins, a

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1 proportion of the women were referred for colposcopy  
2 based on other clinical indications, such as self-  
3 sample HPV or visual inspection.

4 In China, all patients received colposcopy  
5 and multiple biopsies, and in Portland, not listed  
6 here, verification bias is not really an issue because  
7 the longitudinal follow-up is a substitute for  
8 verification.

9 Now surprisingly, the verification bias is  
10 somewhat different between the first four, in which  
11 all or a random sample of women were selected, and the  
12 last three, in which it was directed. In particular,  
13 the CIN3 column, there was no verification bias in any  
14 of those first four, but there was some in the last  
15 three where there were directed colposcopies.

16 That illustrates the difficulty in  
17 adjusting for verification bias when double negative  
18 women are not randomly referred to colposcopy.  
19 Clearly, while it may be inappropriate to assume zero  
20 bias in the random groups, adjustment based on the  
21 prevalence of disease in the directed groups result in  
22 significant over correction for verification bias.

23 This just summarizes what we have already  
24 talked about, that in China all of the biopsies  
25 performed on double negative patients were negative

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1 for CIN2 and above. Similarly, in Germany, U.K. and  
2 Costa Rica, those patients randomly referred for  
3 colposcopy were all negative.

4 Based on this sample of over 1,500 women,  
5 we have reasonable confidence that verification bias  
6 is minimal. However, as seen in the previous slide,  
7 we know that the bias is not zero.

8 So what approaches were taken in this  
9 application? The primary analysis in the PMA is based  
10 on uncorrected results. Because the focus of our  
11 presentation is on the relative differences between  
12 PAP and HPV, we believe this to be an appropriate  
13 approach.

14 However, in studies where there is  
15 verification bias, the absolute sensitivity of PAP in  
16 the combined tests are, in fact, overestimated.

17 Now, we've only had about two weeks to  
18 digest the extensive FDA statistical review, and less  
19 than 24 hours to review the statistical presentation,  
20 which is slightly different from the original review,  
21 but it appears that the FDA statistical reviewer took  
22 two principal approaches.

23 First, in studies with random colposcopy,  
24 a Bayesian estimate was used in which the verification  
25 bias from each study is used to adjust the outcomes

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1 for that study.

2 It is our view that this is an overly  
3 conservative analysis since the verification bias  
4 adjustments for each study do not take advantage from  
5 all of the information from all of the other studies,  
6 namely, the 1,500 plus women who were confirmed  
7 negative from all of the studies.

8 And this information could be used to  
9 provide a more accurate estimate of verification bias.

10 Second, in studies with directed  
11 colposcopy, the disease prevalence in the verified  
12 group was used for adjustment under the assumption  
13 that the complete double negative population is  
14 accurately represented by the directed colposcopy  
15 population.

16 Again, it is our collective view that  
17 this, too, is an overly conservative assumption. Not  
18 surprisingly the adjustments based on both of the  
19 methods used by the FDA result in large reductions in  
20 sensitivity for both PAP and the combined test, which  
21 also impacts the calculation of the relative  
22 improvements in sensitivity.

23 However, even by this very conservative  
24 criteria, Germany and Mexico were shown to be  
25 successful studies. The FDA review also indicates

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1       that the Portland study was successful, and  
2       significantly the Portland study is the largest of the  
3       eight studies, the principal source of U.S. data, and  
4       the longitudinal study supporting the proposed  
5       diagnostic algorithm.

6               In the remaining five studies, the FDA  
7       analysis showed trends towards significant relative  
8       increases in sensitivity. Based on our consultations  
9       with Dr. Schoenfeld, we believe that there are more  
10      appropriate Bayesian methods to adjust for verification  
11      bias that take advantage of data from all of the  
12      studies and also make more appropriate use of the  
13      directed colposcopy results.

14             Because of the short time frame here we  
15      have only recently completed as a preliminary analyses  
16      and are precluded from providing that information to  
17      the panel. These preliminary analyses show that based  
18      on appropriate adjustments, the results continue to  
19      meet the primary endpoint success criteria.

20             So to recap the key results, specificity  
21      results for both CIN2 and above and CIN3 and above  
22      show that seven out of eight studies meet the success  
23      criteria, and the eighth study exceeded the bound by  
24      only a small amount.

25             The prespecified primary outcome and

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1 success criteria was that the relative increase in  
2 sensitivity for detection of CIN2 and above would  
3 exceed 25 percent. This outcome was met for six out  
4 of seven studies.

5 In the remaining study, the Baltimore  
6 study, which was the smallest study, included because  
7 of its value as U.S. data from a well known  
8 institution; in that study, the combined test  
9 identified all confirmed cases of cervical disease.

10 Moreover, even when the primary outcome  
11 was changed to include only CIN3 and above, as per the  
12 recommendation of the Panel and FDA, the success  
13 criteria was met in six out of eight studies.

14 In the remaining two studies, again,  
15 Baltimore and then China, the combined test identified  
16 all confirmed cases of cervical disease, and in fact,  
17 in China, where every single patient was biopsied, HPV  
18 identified every case of cervical disease.

19 Finally, we believe that the use of  
20 appropriate methods for verification bias adjustment  
21 confirms that the combined test provides significant  
22 benefit compared to PAP alone.

23 In summary, while PAP sensitivity is  
24 highly variable in these studies, the combined test  
25 provides uniformly high sensitivity. Thus, from a

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1 statistical standpoint, in the studies where the PAP  
2 missed the most cases is with the studies with the  
3 best results statistically for the combined test.

4 Note, however, that HPV performed  
5 extremely well in all studies.

6 So in our view, the data presented today  
7 constitute valid scientific evidence providing  
8 reasonable assurance of the safety and effectiveness  
9 of the Digene hybrid capture II (phonetic) HPV test as  
10 an adjunct to PAP smear in the evaluation of cervical  
11 disease.

12 Thank you.

13 DR. KILLACKEY: Good morning. Let me  
14 bring you back to the clinic, to the patient.

15 My name is Maureen Killackey. I don't  
16 have any financial investments or interests in Digene.  
17 I've never been a speaker or investigator or  
18 consultant for them.

19 What I am, however, is a GYN oncologist,  
20 and I have 20 years of experience, 18 in New York  
21 City, and now for the past two years as Director of  
22 our regional cancer program in Cooperstown, New York,  
23 a very rural experience. But that experience also  
24 brings with it treating too many women, frankly, too  
25 many women with cervical cancer.

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1 I guess I do have a vested interest today,  
2 however, in appearing here, and that is that I am a  
3 provider. I am a clinician, and most important I also  
4 consume of these services, and with that in mind, I,  
5 too, bring in some clinical perspectives.

6 From the experience of a PAP smear screen  
7 for the past 60 years, we've been able to identify and  
8 describe women who we would describe as being high  
9 risk to develop cervical neoplasia. However, this  
10 kind of diagnosis or description probably brings in  
11 most American women based on those criteria of having  
12 sex at an early age, multiple sexual partners, or  
13 being exposed to your male partner with multiple  
14 partners.

15 Therefore, we clearly need to better  
16 refine the definition of high risk woman. We need to  
17 refine it in order so that we may focus our screening  
18 resources.

19 Presently PAP smear screening in the  
20 United States is less than perfect. Dr. Kinney has  
21 described that there are variations in guidelines.  
22 There's no concordance among subspecialty groups about  
23 when to start screening, when to stop screening, or  
24 the intervals.

25 PAP smear providers, there are a multitude

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1 of specialists, nurse practitioners, family  
2 practitioners, as well as OB-GYNs obtaining the 50  
3 million PAP smears that are sent in the United States  
4 annual. Not all providers have the time or the  
5 expertise to understand the nuance of the subtleties  
6 of the PAP smear report.

7 And finally, there clearly are limitations  
8 to conventional dry slide cytology. The findings from  
9 the AHCPR data that conventional PAP has a 51 percent  
10 sensitivity are sobering. Therefore, we really need  
11 to make a good test, a good cancer screening test,  
12 even better. We need to focus our screening efforts  
13 and provide an acceptable testing scheme for the  
14 patients and providers.

15 With this proposed combined testing  
16 proposal, women over 30 who are HPV positive and PAP  
17 smear negative will now be identified as the high risk  
18 group. There clearly is potential that without  
19 adequate education of providers and patients that  
20 there may be inappropriate colposcopy referrals, over  
21 treatment, unnecessary surgery.

22 This must be avoided by a concerted  
23 educational effort specifically to educate people  
24 about the natural history of HPV infection. Again,  
25 very specifically, the significance of a positive HPV

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1 high risk result in a woman over the age of 30; that  
2 is not a transient infection. That is a condition  
3 that connotes or confers a significant risk to develop  
4 cervical neoplasia.

5 With this in mind, we can better define  
6 the high risk woman and, again, focus on this very  
7 small group of women that will need more diligent  
8 screening.

9 How about for the patient? And that's  
10 what we're here for, after all. Clearly, as anyone  
11 who has participated in January in the Cervical Health  
12 Awareness Month, and we certainly did in upstate New  
13 York, going to ten counties, and we had many programs  
14 for this; there clearly is a major need to educate the  
15 public.

16 The public is the patient, but the public  
17 is also the parents, the kids in the high schools; to  
18 educate them about the fact that cervical cancer is a  
19 sexually transmitted disease. So education is very  
20 important.

21 With education, knowledge will result, and  
22 knowledge is clearly power. Women then will be able  
23 to control their risk factors.

24 We can also now with this proposal being  
25 adapted, we can now reassure patients that -- and it's

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1 clear to the public that the PAP smear is less than a  
2 perfect test -- we can now start to reassure the  
3 public that a combination of HPV testing along with  
4 PAP smear screening will increase the sensitivity of  
5 this test. What that means is that we as providers or  
6 we as consumers, when we get our PAP smear and invest  
7 our time, emotional energy and the cost of the visit,  
8 we can get and are assured that we will have the most  
9 accurate screen.

10 How will these results relate to the  
11 patient? The HPV negative woman and PAP smear  
12 negative woman, and this will be the majority of  
13 women; greater than 90 percent of American women will  
14 be in this category.

15 We can clearly reduce their anxiety and  
16 reinforce their lowest behavior, that is, put them  
17 into this good category.

18 For the high risk patient or the HPV  
19 positive, PAP smear negative patient, clearly we as  
20 clinicians have a major input to this, and we must put  
21 it into perspective. Yes, it is a sexually  
22 transmitted disease, but there are millions of other  
23 women who are affected with sexually transmitted  
24 diseases, such as chlamydia, trichomonas, and Herpes.  
25 There is no need to stigmatize HPV infection.

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1           Rather, the emphasis should be on  
2           modification of behavior, eliminating other risk  
3           factors. This would be a tremendous effort to have  
4           smoking cessation programs, especially in the high  
5           school. We clearly can also use this as an emphasis  
6           to stress the need for compliance. What the doctor,  
7           what the provider tells you to do for follow-up in PAP  
8           smears, if we say a year, we mean 12 months. We don't  
9           mean 17.

10           Finally and in conclusion, adoption of  
11           this proposal will clearly have a benefit to patients  
12           and to providers. We as clinicians can now base our  
13           decisions on more objective measurements rather than  
14           subjective criteria or variations in the cytology lab  
15           of the HMO choice. We will now be able to identify  
16           those women who need more frequent screening. We can  
17           reassure the vast majority of HPV negative women. We  
18           can reinforce their low risk behavior, and confidently  
19           perhaps even say that you can be screened every three  
20           years safely and confidently.

21           Thank you very much for your time.

22           DR. COX: I'm Tom Cox. I'm coming to you  
23           as a clinician and as an individual who has been  
24           intensely interested in studying clinical utility of  
25           HPV testing, which I've been doing for about the last

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1 14 years.

2 I've also participated in multiple  
3 guideline committees in drawing up guidelines for PAP  
4 smear management.

5 I have no financial interest in Digene.  
6 I have occasionally been supported in educational  
7 endeavors just as Dr. Kinney has.

8 I think we all understand the central fact  
9 of cervical cancer causation, that for most women who  
10 harbor detectable levels. One of two things will  
11 happen. Either they will clear HPV, and most of them  
12 will clear HPV, or they will develop CIN.

13 I'll be presenting an algorithm here for  
14 management of individuals tested by both HPV and  
15 cytology, which I believe will be maximizing the  
16 detection of the latter and minimizing those of the  
17 former, and that is because this algorithm will take  
18 into account the following clinical parameters for HPV  
19 testing that are really well documented in the  
20 literature.

21 That only persistent, high risk HPV  
22 infection leads to CIN2+;

23 That HPV detection in women greater than  
24 age 30 is more likely to represent persistent  
25 infection;

1                   And that the positive predictive value of  
2                   HPV DNA for the detection of CIN rises with age,  
3                   whereas that cytology decreases.

4                   What we know is that in the end it is a  
5                   combination of success of the virus in invading the  
6                   immune system and its ability to exert influence over  
7                   normal post gene expression that determines the  
8                   emergence and persistence of CIN3.       Therefore,  
9                   persistent HPV is a necessary prerequisite for HSIL  
10                  and for subsequent risk for invasive cancer.

11                  There are several issues that came out in  
12                  the eight studies that were evaluated here that are of  
13                  great clinical relevance. One is it was very obvious  
14                  looking at the charts that Dr. Lorincz put up that the  
15                  subjectivity and variability in the reading of  
16                  cytology is quite great, and it is demonstrated by the  
17                  wide range of PAP sensitivity reported across the  
18                  eight studies, that range being 34 to 97.6 percent.

19                  Additionally, in contrast, all studies  
20                  demonstrated very high sensitivity for the HPV test  
21                  and demonstrated clinically meaningful improvement in  
22                  sensitivity with the subjunctive HPV testing.

23                  Substantial improvement was also realized  
24                  in several studies in this data set that had PAP  
25                  sensitivities compared with that in the U.S.

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1                   Additionally,     all     eight     studies  
2     demonstrate   clinically   acceptable   reduction   in  
3     specificity with adjunctive HPV testing.

4                   Now, this has been mentioned before, but  
5     I think it needs to be discussed further.   There's  
6     only one organization in the United States that  
7     recommends annual PAP screen no matter what risk  
8     factors, and that is the College of American  
9     Pathologists. All the other organizations that you  
10    see here have recommended that after two to three  
11    normal annual PAPs, that the interval for screening  
12    may be increased, and that interval increase is  
13    documented below to be from one to three years or two  
14    years or for some at least every three years, and for  
15    Canadian National Workshop report, a three year  
16    interval is recommended.

17                   All of the above are recommended at the  
18    discretion of the clinician and are said to be based  
19    on risk factors. We've seen these risk factors  
20    before, that high risk women should be screened more  
21    frequently than low risk women, and the definition of  
22    high risk was based, as Dr. Kinney said, on historical  
23    factors that do not have a great deal of accuracy.

24                   They're also on issues that we often  
25    cannot discern whatsoever.       Early onset of

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1 intercourse, less than 18, history of multiple sex  
2 partners, those two issues alone put most women or the  
3 majority of women in the category of high risk for the  
4 rest of their lives.

5 Low socioeconomic status,  
6 immunodeficiencies, smokers, and previous dysplasia  
7 without five annual within normal PAPs, tolerant  
8 dysplasia (phonetic) are also mentioned.

9 But the one that most trips all of us up  
10 as clinicians in determining risk is a woman who has  
11 a partner with multiple sex partners, but we never the  
12 sex history of an individual's partners. As a result  
13 of that, we have not been able to really categorize  
14 women adequately as low risk and put them into the  
15 screening guidelines that have been recommended for  
16 women that are not at high risk.

17 I would like to say that with HPV testing  
18 with cytology, we now have the first objective risk  
19 stratification for which women really are at higher  
20 risk, but we know now that higher risk women are those  
21 that are HPV positive, and those that are HPV  
22 negative, PAP negative, truly are at low risk for  
23 disease.

24 So with this in mind, we propose the  
25 following diagnostic algorithm: that HPV testing and

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1 PAP smear be used only for women 30 and over, and that  
2 those that are cytology negative, but HPV positive are  
3 at a higher risk and should have HPV and PAP follow-up  
4 within 12 months, whereas those that are HPV negative  
5 and PAP negative are definitively at lower risk and  
6 may be screened according to routine screening  
7 practice recommended already by all of these  
8 organizations for low risk women.

9 The management of abnormal PAP smears with  
10 HPV testing results has really not changed from  
11 present guidelines for management of abnormal PAPs.

12 There are several safety considerations  
13 that have been raised. We are not recommending HPV  
14 positive, PAP negative women to be referred to immediate  
15 colposcopy unless there are clinical factors that make  
16 that person of concern. A good example would be an  
17 abnormal appearing cervix, for instance.

18 The consequence of a, quote, unquote,  
19 false positive is not a necessary and expensive  
20 colposcopy and biopsy, but more diligent surveillance  
21 within recommended screening time frames. Remember  
22 that a positive HPV test places a risk stratification  
23 on these individuals that allows us to know that they  
24 need to be followed more carefully. I would not call  
25 that, therefore, a false positive test.

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1 Safety concerns should be minimized with  
2 proper labeling on how this test should be used, and  
3 with physician education, and those of us involved in  
4 physician education will be very actively involved in  
5 getting these points across.

6 Thank you.

7 MR. KAHN: Thank you very much.

8 My name is Jonathan Kahn. I'm a partner  
9 with the law firm of Hogan & Hartson, and we are  
10 regulatory counsel to Digene.

11 We have probably about 15, 17 minutes more  
12 to go. You'll be happy to hear I only intend to take  
13 two and a half minutes. So we will end the Digene  
14 presentation a little bit early.

15 First, let me say we've been trying to  
16 work with Digene and the FDA for almost two years now  
17 to figure out how best to present this to the agency  
18 and to the panel, and there has been, as you probably  
19 can tell from the presentations today, an incredible  
20 amount of work that has gone into trying to present  
21 this in a reasonable and rational way that will both  
22 serve the needs of the public health and provide the  
23 data that you and FDA need to make an educated  
24 judgment.

25 I think that it's best to say that we

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1 started out not at the book of Genesis. I think we're  
2 fortunate in that we already have an approved device  
3 that has I think it's safe to say been generally  
4 recognized by FDA and the scientific community that  
5 the test is accepted as a valuable tool to follow up  
6 and screen women with ASCUS PAP smear results to  
7 determine the need for colposcopy, as well as in the  
8 management of women who have LSIL and HISIL (phonetic)  
9 cytology results by assisting with risk assessment to  
10 determine the absence of high grade disease.

11 Therefore, we are today really doing no  
12 more than seeking the panel's consideration and FDA's  
13 approval of an expanded screening plan for the use of  
14 HPV adjunctively with PAP. And I think we want to  
15 make it clear that this is not a substitute for PAP  
16 under the labeling presented by the company. Digene  
17 strongly believes that it has demonstrated today that  
18 adjunctive HPV testing provides a clinically important  
19 increase in sensitivity with an acceptable decrease in  
20 specificity.

21 This demonstration was based upon an  
22 analysis of existing study data rather than a  
23 prospectively designed 45,000 patient study to try to  
24 prove this to the panel, to FDA. We believe that this  
25 was a common sensical approach. One could imagine

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1        what would go into prospectively designing a single  
2        protocol, multi-center, 45,000 patient study.

3                    It has -- since the passage of the medical  
4        devices amendments of '76, I don't remember an IB --  
5        I've been doing this 27 years, but I don't remember an  
6        IBD that had that kind of data prospectively designed.  
7        So the company decided let's look at what's a  
8        scientifically valid way to go utilizing the line data  
9        from existing studies.

10                   And the company, I believe, thinks that  
11        the benefits were clearly demonstrated in the U.S.  
12        population by the Portland study, and that the foreign  
13        studies provided a complementary support for the very  
14        strong U.S. data.

15                   Was the reliance on these multiple studies  
16        sometimes with differing methodologies a perfect  
17        model? I think the answer is no, but remarkably, even  
18        with the differences in the studies, the results  
19        consistently showed a relatively improvement of  
20        sensitivity essentially independent of population  
21        differences and disease prevalences, and therefore, we  
22        believe that the approach of using multiple studies,  
23        while not what you see every day before this panel, is  
24        a very appropriate scientifically valid way to  
25        proceed.

1           The eight diverse clinical studies  
2 provided valid scientific evidence supporting safety  
3 and efficacy for this adjunctive claim under the  
4 labeling that you have already in your packages. The  
5 supporting data we believe are certainly strong enough  
6 so that a clinician, based upon his or her review of  
7 the study data, can make an educated decision to  
8 recommend or not recommend adjunctive HPV screening in  
9 the identified population of women.

10           We believe that the recommended diagnostic  
11 algorithm just discussed by Dr. Cox is consistent with  
12 current screening guidelines. We're not asking for  
13 any kind of revolutionary change in screening  
14 interval. All we're saying here is that this is  
15 valuable information which we believe the clinician  
16 should have available to them through the Digene label  
17 so that the clinician can make an educated judgment as  
18 to how best to treat the women.

19           In sum, we believe the data support the  
20 expanded labeling claim and are more than sufficient  
21 to support the panel recommendation of approval today.

22           Thank you very much.

23           CHAIRMAN WILSON: Thank you.

24           Before we open the discussion up to  
25 questions, I'd like to introduce Dr. Mel Weinstein

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1 from Robert Wood Johnson in New Jersey. Mel was kind  
2 enough to travel down early this morning, but his  
3 travel arrangements got him in a few minutes late, but  
4 welcome.

5 So at this point I'd like to open the  
6 discussion up for questions for members of the panel  
7 to ask questions of Digene. I'm not sure that I'm the  
8 best one to do this particular discussion. Perhaps  
9 Dr. Kinney, who looked at this in the Kaiser system  
10 could approach this better, but I think that under the  
11 guidelines that have been given to us in terms of  
12 allowing us to increase the screening interval for  
13 women who are considered low risk, that the  
14 sensitivity of the PAP smear as such, which is in the  
15 range of 50 percent for all CIN and probably in the  
16 range of 75 to 80 percent maximum for high grade CIN  
17 has not given us the reassurance that we needed to be  
18 able to screen comfortably women at longer intervals.

19 I'm concerned that with that kind of false  
20 negative potential that if we were screening women  
21 every three years we would not be able to have the  
22 reassurance that perhaps missing 25 or more percent of  
23 individuals at each screening might over a period of  
24 six to nine years for some individuals result in  
25 undetected, progressively to become basic cervical

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1 cancer.

2 Do you have anything to add to that,  
3 Walter?

4 DR. KINNEY: I wasn't involved in the  
5 discussions about what the precise numbers should be.  
6 However, it's been clear to us from our experience  
7 with implement the guideline that involved extension  
8 from annual screening of this to longer intervals that  
9 this was nothing something that either the clinicians  
10 or the patients were comfortable with, and the more we  
11 examined that based on our own data, the more we felt  
12 that their concerns were meritorious.

13 In addition, looking at the number of  
14 cancers that we felt represented the false negative  
15 consequences, the false negative rate for PAP, any  
16 improvement in sensitivity would be most welcome both  
17 in terms of reducing our cancer rates and in terms of  
18 reassuring patients and the providers that we would  
19 provide an optimum service to them.

20 DR. COX: Just one more statement. I  
21 think one of the things that's so obvious in looking  
22 at this data is that in all of these studies, and  
23 you've been involved in HPV testing as well. So I  
24 know you understand this, that there is an objective  
25 reliability in this test. It has a very high

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1 sensitivity across the board. It doesn't vary from  
2 one lab to another on any great basis in contrast to  
3 psychology.

4 So this very, very high sensitivity gives  
5 us a degree of reassurance that no matter what the  
6 actual absolute separation agreement happens and the  
7 HPV tests from one lab to the other, in some labs it's  
8 going to be a huge difference. In some it's going to  
9 be less, but it's that consistent non-variability test  
10 that gives us the reliability that we need to be able  
11 to feel more comfortable.

12 It's screening within these guidelines  
13 that are actually promulgated around these  
14 organizations.

15 CHAIRMAN WILSON: Dr. Noller.

16 DR. NOLLER: It's reasonably well known  
17 that even the high grades and CIN can spontaneously  
18 disappear. Perhaps 20 percent or so of CIN2 and a  
19 smaller number, maybe ten percent of CIN3 lesions can  
20 disappear without any treatment whatsoever.

21 Do you have any information to show that  
22 the additional CIN lesions that you identify with the  
23 addition of the hybrid capture II to routine screening  
24 finds lesions that persist or progress rather than  
25 just transient infections that would spontaneously

1 disappear?

2 More simply, are you just identifying  
3 lesions that are going to go away and are meaningless  
4 clinically or are you identifying true disease?

5 DR. COX: I don't think that any of the  
6 world literature helps us on that a great deal, and  
7 therefore, anything we do to improve detection is  
8 always with the understanding that we're going to pick  
9 up some high grade lesions that might have  
10 disappeared, but that's true with PAP smear screening  
11 as well.

12 We're going to pick up lesions that might  
13 disappear because we cannot predict at this point in  
14 time which lesions will progress or which lesions will  
15 not progress. We really have to pick up all of them,  
16 I believe, to treat them.

17 There may be at some point in history  
18 markers which help us better determine which lesions  
19 will be progressive, but those are not available to  
20 help any of us at this point in time.

21 CHAIRMAN WILSON: Dr. Berry.

22 DR. BERRY: A question for Dr. Cox or Dr.  
23 Killackey.

24 You said that these are not false  
25 positives when the PAP smear test is negative and the

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1 HPV is positive. I understand your point, but what  
2 does the woman -- I mean, isn't the woman adversely  
3 affected by that?

4 DR. KILLACKY: This clearly is where  
5 education -- and it is going to be education,  
6 providers and patients -- is going to have to be very  
7 clear. The presence of HPV positivity in the setting  
8 of a negative PAP smear means that at some point she  
9 was infected by a high risk virus, and it was as  
10 simple as that, and that's what we explain to the  
11 patient.

12 I think we have to explain to the patient  
13 that colposcopy biopsies are not necessary at that  
14 time; that the persistence of this infection is what  
15 really counts, and that's what confers her risk. It's  
16 something, again, that it will take some time  
17 explaining to the patient, but women are smart.  
18 They'll get it.

19 DR. COX: Yeah, I'd like to add a little  
20 bit to that as well. Over the last two or three  
21 years, there's been a great increased interest in all  
22 of the media regarding HPV. It's really been like a  
23 still STD before this. People didn't know about it,  
24 but it's really gotten out there.

25 It's been on MTV. It's been on most of

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1 the women's magazines over and over. It's been in the  
2 newspapers. Women are getting very educated on this,  
3 and that will continue to increase.

4 What I think is important for us to always  
5 emphasize, and I always do this when I interview  
6 regarding media events or articles, is that most of  
7 the literature would give us a great deal of  
8 information now and reassurance or not reassurance,  
9 depending on how you look at it, that getting HPV is  
10 almost a part or synonymous with sexual activity; that  
11 individuals who are sexually active have a very high  
12 risk of getting this once or more times in their  
13 lifetime, and for most individuals this is a transient  
14 event with no significant long-term consequences.

15 And as long as you educate women that that  
16 is the case, that it is not a great threat to get  
17 this, it does indicate that until they are followed  
18 and found to not have anything by virtue of having the  
19 virus disappear or disease detected and treated on  
20 follow-up if as necessary, that there is nothing for  
21 them to be greatly concerned about this, and I think  
22 that message can be gotten across with good education.

23 CHAIRMAN WILSON: Dr. Lorincz?

24 DR. LORINCZ: Excuse me, but I would like  
25 to make a couple of clarifications for the previous

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1 questions, which I believe were not answered totally  
2 adequately.

3 First, to the question from Dr. Koutsky.  
4 The 25 percent range we felt was a reasonable and  
5 logical number, but if you recall looking at the data  
6 most of those relative increases were much, much  
7 greater than 25 percent, around the order of 50 or 70  
8 or 100 percent, and so we felt that that was a logical  
9 number to choose.

10 And perhaps we can debate it further, but  
11 I think that the clinicians agree that as a first  
12 principle if that's exceeded that's a justifiable  
13 increase.

14 Number two, from Dr. Noller saying three  
15 detected by HPV, firstly, we're not recommending  
16 colposcopy on the basis of an HPV positive result. If  
17 you recall the algorithm, it says repeat the PAP smear  
18 within the year for those women who are HPV positive.

19 Therefore, if the women is HPV, is PAP  
20 abnormal, she gets the colposcopy on the basis of  
21 normal PAP considerations. There is little to no  
22 evidence that most CIN3 goes away in any event. It is  
23 either persistent or progressive.

24 And the last point is that there are  
25 numerous studies in the literature that demonstrate

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1       that CIN3+ detected by HPV is not different than CIN3+  
2       detected by PAP smear or any other method, and these  
3       appear similar morphologically. Their progression and  
4       regression rates are the same.

5               So I would counter that there's no  
6       evidence that there is a difference in those. In  
7       fact, virtually all CIN3 is HPV positive. So I think  
8       the one that have the tests are cumulatively a subset,  
9       but eventually PAP detects them all as well over many  
10      repeated years.

11             That's all I wanted to say.

12             CHAIRMAN WILSON: Dr. Felix?

13             DR. KOUTSKY: If I could just -- how about  
14      just your thinking behind a ten percent decrease in  
15      specificity?

16             DR. LORINCZ: Well, both the 25 percent  
17      increase, relative increase in sensitivity and ten  
18      percent increase in specificity were numbers that we  
19      had discussed at the FDA and had not been raised as  
20      unreasonable numbers.

21             For the sake of argument, I would say that  
22      most of the studies did not show anywhere close to a  
23      ten percent decrease in specificity. The combined  
24      loss in specificity for PAP and HPV for most of the  
25      studies was on the order to two to three percent.

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1                   Again, we feel that that is a reasonable  
2                   loss, and one needs to take a rational balance to this  
3                   and recognize that we're using very strict criteria.  
4                   Women who are HPV positive, but who have no detectable  
5                   disease are, in fact, as mentioned by previous  
6                   speakers not false positives because longitudinal data  
7                   demonstrate that persistent HPV positivity ends up  
8                   turning into high grade disease if those women are  
9                   followed.

10                   So I think that one has to take the  
11                   decrease in specificity in a reasonable context to  
12                   recognize that at a minimum those women who are HPV  
13                   positive are at higher risk, and we are recommending,  
14                   therefore, that they should be followed rigorously by  
15                   at least annual PAP smear screening and should not be  
16                   allowed to go to the longer screening intervals.

17                   So we feel that that is a rational  
18                   approach to the decrease in specificity issue. Okay?

19                   DR. FELIX: I'm Juan Felix.

20                   Tom, both you and Walter mentioned at  
21                   least as one of your rationales that clinicians have  
22                   been uncomfortable prolonging the screening interval,  
23                   relying on a PAP smear that had a poor sensitivity for  
24                   detecting disease. You mentioned that the increase in  
25                   sensitivity with an added test, such as HPV, might

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1 facilitate that.

2 And, in fact, Dr. Lorincz has mentioned  
3 that in HPV positive, PAP negative women you would  
4 follow at yearly intervals.

5 Now, there is nothing in the submission  
6 that I read that mentions prolonging screening  
7 intervals at all. Why is it important -- if it's  
8 important as a strategy, there's a little bit  
9 discrepancy between this mission, what is being asked  
10 for or proposed, and what you're arguing for,  
11 prolongation of screening intervals, isn't there?

12 DR. FLEISCHMANN: Yeah, I think if you  
13 look at that algorithm we presented, it doesn't say  
14 anything about prolonging screening at all. It says  
15 that it allows us to assume intervals that are  
16 suggested by these guideline committees for low risk  
17 women.

18 That would be at the discretion of the  
19 clinician to decide what interval that was, but all it  
20 does is allows us to do what has already been  
21 promulgated by all of these guideline committees for  
22 women that have been designated to be low risk, and I  
23 would be surprised if -- I mean, I would suspect that  
24 most here would understand that the literature really  
25 seems to give us a great deal of reassurance that a

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1 double negative is somebody who's at low risk at that  
2 point in time.

3 DR. FELIX: Well, I realize that. You  
4 know, your argument is good. I favor the argument.  
5 It's just that there's nothing in the submission that  
6 specifies the prolongation of screening as a target.

7 DR. FLEISCHMANN: If I could respond, we  
8 are not recommending expanding screening intervals.  
9 All we're saying is that for the HPV positive -- HPV  
10 negative, PAP negative woman, the physician can do  
11 that within his or her management of low risk women.

12 CHAIRMAN WILSON: Dr. Koutsky.

13 DR. KOUTSKY: To follow through the  
14 algorithm, so a woman's PAP negative, HPV positive and  
15 she comes back within 12 months, and let's say she's,  
16 again, tested with PAP and HPV or do we continue on  
17 and see what happens with these people? What are the  
18 alternatives?

19 If she comes back within 12 months, what  
20 are the different alternatives for her?

21 DR. COX: The algorithm actually said PAP  
22 and HPV in 12 months, not just PAP.

23 Well, obviously --

24 DR. KOUTSKY: Then if it's PAP, it's PAP  
25 and HPV, and she's negative for PAP, positive for HPV.

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1 DR. COX: Positive for HPV. Well, I think  
2 that the guidelines' recommendations will be drawn up  
3 for those issues. I would say that from a personal  
4 standpoint in a woman over the age of 30 who was  
5 consistently positive over a year's time at two  
6 different points in time, I would want to colposcope  
7 that woman, but that's my own professional opinion,  
8 and believe that it would be up to the individual  
9 practitioner to decide at that point in time whether  
10 this resulted in continued close follow-up or whether  
11 it resulted in colposcopy.

12 DR. KOUTSKY: Okay. Then in the group  
13 that is PAP and HPV negative at screening and let's  
14 say their clinician does recommend screening every  
15 three years. Is it no being that they would then  
16 every three years be screened by both PAP and HPV?

17 DR. FLEISCHMANN: I would believe so, yes.

18 CHAIRMAN WILSON: Dr. Felix.

19 DR. FELIX: So in your management scheme,  
20 Tom, or in the one that is being advocated, the new  
21 category of PAP negative, HPV positive does not result  
22 in colposcopy?

23 DR. COX: That's right.

24 DR. FELIX: And is that a change in  
25 current management?

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1 DR. COX: Well, right now current  
2 management doesn't typically use HPV testing and PAP  
3 in conjunction in routine screening. So this is a --

4 DR. FELIX: But that would be a PAP  
5 negative patient.

6 DR. COX: It's a PAP negative patient.

7 DR. FELIX: So she would go to following  
8 annual screening?

9 DR. COX: She would go to a screen within  
10 the next 12 months.

11 DR. FELIX: With or without HPV  
12 positivity?

13 DR. COX: I'm sorry. I didn't understand  
14 that.

15 DR. FELIX: In other words, for most women  
16 who are screened in the United States, they're  
17 screened on an annual basis.

18 DR. COX: That's right.

19 DR. FELIX: I beg your pardon?

20 DR. COX: That is true, but for the  
21 reasons that I've already stated they're screened on  
22 an annual basis because they have not been able to  
23 restratify individuals correctly on the basis of  
24 historical data.

25 DR. FELIX: Again, okay. It just means to

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1 me that the proposed emphasis is that if the new test  
2 allows for prolongation of screening by the clinician  
3 because if you're going to screen yearly, it doesn't  
4 make any difference whether it's PAP positive or  
5 negative.

6 DR. LORINCZ: I'd like to clarify this  
7 point because I think it's very important. We are  
8 saying that the HPV test provides additional  
9 information to base a risk stratification of women.  
10 It does not result in a change in any of the  
11 guidelines.

12 Currently within the guidelines already  
13 exist the option for risk stratification and longer or  
14 shorter intervals. These are based on subjective  
15 measures, such as number of sex partners, coincident  
16 STDs, whatever you may have.

17 What we're saying is that an HPV test is  
18 a more objective measure of the risk for that  
19 particular woman because it tells the clinician and  
20 the woman what is on the cervix that might be related  
21 to future risk of cervical cancer.

22 So, therefore, I think it's important to  
23 take it in the context of additional information which  
24 is subsequently used at the discretion of the  
25 clinician as they see best fit in their judgment

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1 following the guidelines.

2 DR. KILLACKEY: Just to clarify, Dr.  
3 Felix, the CDC data, I think, shows that 70 percent of  
4 women have had a PAP smear from the past 12 to 18  
5 months, that 70 percent of American women get PAP  
6 smears within 12 to 18 months, and for three year  
7 screenings about 85 percent of American women.

8 So by no means does the American woman get  
9 a PAP smear every year. Clearly she can't. There are  
10 50 million PAP smears done in this country. There are  
11 more women than that who should be eligible for them.

12 So we aren't doing annual screening. I  
13 think part of our premise as clinicians and people out  
14 there, as Dr. Cox clearly indicated, is we don't start  
15 with the premise that most women who come into our  
16 offices are high risk just based on the fact that  
17 they're heterosexually active. Unfortunately the age  
18 of first intercourse in this country for young girls  
19 now, 15; for boys it's 14. The fact is early sex is  
20 predominant in this country. So early sex, multiple  
21 partners, or if you've been monogamous as a woman, who  
22 your husband or your partner brings to you.

23 So we all start with the premise that  
24 people are high risk. Therefore, we really want  
25 annual PAP smear screens. This proposal would allow

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1 us to relax those standards and go with the guidelines  
2 that ACOG and many other people say, that you're back  
3 to getting low risk. If you are low risk based on HPV  
4 negativity, you could then be screened every one to  
5 three years at the discretion of your clinician.

6 CHAIRMAN WILSON: Okay. We have time for  
7 one or two more questions. I think Dr. Nolte was  
8 next.

9 DR. NOLTE: Yeah, I'd like to bring it  
10 back to the laboratory for a second, and talk a little  
11 bit about the performance characteristics of the test.  
12 I know this isn't a new device, but basically this is  
13 a test without a gray zone. It's positive or  
14 negative, and I'm a little concerned about applying  
15 this widely as a screening test without -- in order to  
16 keep the specificity appropriate.

17 Is there some way to deal with the  
18 information that you get from, let's say, the  
19 quantitation, the relative light units or the level of  
20 positivity? Because that can improve the performance  
21 characteristics in terms of reducing false positives.

22 DR. LORINCZ: You're correct in the  
23 statement that there is no gray zone in this test. We  
24 chose a single cutoff of one picogram per mL, and any  
25 result that gave a stronger signal than that was

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1 positive. Any specimen that gave a result below that  
2 was negative.

3 Some other tests do have gray zones. We  
4 felt that it was unnecessary to establish a gray zone  
5 because the test is highly reproducible as  
6 demonstrated in the FDA submissions and approvals for  
7 ASCUS triage and also in the current submissions.

8 The false positives that you allude to,  
9 firstly, we want to be careful about that term because  
10 we do not believe that there is any substantial number  
11 of HPV false positives. The test itself is very, very  
12 reproducible in terms of demonstrating the presence of  
13 absence of the virus itself. What we are loosely  
14 calling false positive here is the interpretation of  
15 an HPV positive in a woman who does not appear to have  
16 disease.

17 DR. NOLTE: No, I understand that. I'm  
18 really focused at the level of the testing.

19 DR. LORINCZ: Correct, correct. Okay. So  
20 in terms of quantitation, we od not have any claims  
21 pending for that. We have not attempted to put  
22 quantitative claims into the assay, into the kit at  
23 the current point in time because we feel that the  
24 data are insufficient.

25 And additionally, there does not appear to

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1 be a strong correlation between the apparent levels of  
2 virus and the probability of specific categories of  
3 disease. So we felt that the best compromise was to  
4 establish a minimum cutoff level above which the  
5 probability of disease was maximized and below which  
6 it was minimized and that this should be as much as  
7 possible maximizing the sensitivity sine in developed  
8 countries emphasis on sensitivity seems to be the  
9 predominant criterion, and that was the rationale that  
10 we followed in developing our test and in setting  
11 cutoffs.

12 DR. NOLTE: But you do understand my  
13 concerns that now we're switching the application of  
14 the test from a population that's enriched for disease  
15 to a population that's essentially the disease is  
16 going to be --

17 DR. LORINCZ: That's correct, and I  
18 believe that the data we showed in the screening  
19 context demonstrated that the decrease in specificity  
20 being only a few percent was a rational, reasonable  
21 number to accept in exchange for the dramatic increase  
22 in sensitivity provided by the test.

23 So we, in fact, have given you the exact  
24 data that you would expect in terms of how much the  
25 specificity would decrease.

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1 DR. NOLTE: And just one other point.  
2 There are several of the publications and references  
3 in the back that you provided that allude to the  
4 quantitative aspect of the test, and as you said,  
5 there's not a strong correlation between the quantity  
6 of HPV detected and disease state.

7 But is that data available for the  
8 studies? The quantitative data, is that available for  
9 the eight studies?

10 DR. LORINCZ: The quantitative data can be  
11 available for all of those eight studies, in fact, and  
12 there are other papers that are being submitted and  
13 are in consideration in the scientific literature  
14 based on viral load, but those are scientific  
15 endeavors meant for the scientific community, and we  
16 chose to not present them here at this time.

17 CHAIRMAN WILSON: And the last question,  
18 Dr. Tuazon.

19 DR. TUAZON: I was addressing the same  
20 issues about the quantitation and correlation of  
21 disease occurrence.

22 CHAIRMAN WILSON: Okay. Thank you.

23 I'd like to thank Digene for their  
24 presentation this morning and for helping keep us on  
25 schedule.

1 At this point I'd like to take a break.  
2 Let's reconvene at 10:45 .

3 Thank you.

4 (Whereupon, the foregoing matter went off  
5 the record at 10:30 a.m. and went back on  
6 the record at 10:52 a.m.)

7 CHAIRMAN WILSON: At this point we'd like  
8 to continue the meeting. We're going to begin with a  
9 presentation from one of our members of the Panel, Dr.  
10 Elizabeth Unger, who's the Chief of the Human  
11 Papillomavirus Section at the National Center for  
12 Infectious Diseases in the Centers for Disease  
13 Control.

14 Dr. Unger.

15 DR. UNGER: Thank you.

16 I'm going to just review a little bit  
17 about HPV. This will be familiar probably to  
18 everybody. I'm just going to try to hit the high  
19 points in order to put everybody on the same page.

20 But a little bit before I start about HPV.  
21 I've like to remind us and ask the Panel to keep in  
22 mind that not only are we talking about human  
23 papillomaviruses, but about cervical cancer screening  
24 and screening programs in cytology of the cervix has  
25 been extremely effective, to the point where a

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1 reduction in cervical cancer has been estimated to be  
2 about 80 to 90 percent with current strategies.

3 So we're left with a situation of trying  
4 to approve what is a good situation, and the positive  
5 predictive value is probably the best guide that we  
6 have to evaluating the efficiency of screening  
7 programs.

8 Our attention is turned to human  
9 papillomaviruses, and while we've been talking about  
10 them like they're an entity, they really are viruses.  
11 There's more than 100 types, and at least 80 have been  
12 fully sequenced.

13 The typing is confusing. It's based  
14 strictly on the nucleic acid sequence, and the  
15 numbering was based on the order that they were  
16 discovered. So there's actually no relationship to  
17 phylogeny.

18 Because of the typing, if there's more  
19 than a ten percent sequence variation it is considered  
20 a new type, and you'll hear things called variance,  
21 and that's types that have less than two percent  
22 difference in the sequence.

23 There are more than 30 different types  
24 that are found in the anogenital (phonetic) tract.  
25 They've been broken down traditionally into low risk

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1 and high risk types, and the lowest types are those  
2 that are rarely found in cancers, and high risk types  
3 are those that are frequently found in the cancers or  
4 in those precursors that are associated with cancer.

5 What needs to be kept in mind, that the  
6 high risk is perhaps a little bit of a misnomer  
7 because the high risk types are really those that are  
8 most prevalent in the general population regardless of  
9 the disease status.

10 Now, the variance which I mentioned, as  
11 the subtypes have been really been best characterized  
12 only for HPV 16, and the significance of these  
13 variances is still an area of significant  
14 investigation.

15 There are some really unique features of  
16 HPV, and one of the most important is that there's  
17 really no simple culture method and the antibody  
18 methods that are currently available lack sensitivity.

19 Therefore, it's a situation that's fairly  
20 unique. Diagnosing the infection requires detection  
21 of HPV genetic information.

22 So as a corollary to this, we have to  
23 really focus very carefully on the sample because it  
24 requires a cellular sample that has to involve the  
25 site of the infection, and because of this, another

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1 fact that only current infections are identified with  
2 this approach.

3 And we're left with the fact that we have  
4 to use infection with a kind of a quotation mark  
5 because what we're really doing is monitoring actually  
6 only DNA detection. The sample and the assay that's  
7 used really frame the view of the disease, and these  
8 considerations complicate definitions of what is a  
9 latent infection, occult infection, persistent  
10 infection, current infection.

11 Now, tissue biopsies are the best direct  
12 correlation between the pathology that's seen in the  
13 virus. These samples include the vasolayer of the  
14 epithelium where infection is believed to be  
15 initiated.

16 They are very limited in the area that's  
17 screened, and biopsies are really not suitable for any  
18 kind of screening studies.

19 Consequently, we have been relying on  
20 exfoliated cervical cytology samples. We know this is  
21 a noninvasive approach for population screen. The  
22 sampling is not directed at the lesion, and there's a  
23 whole variety of ways of coping with cellular  
24 material, including swabs, brushes, scrapes, washing.

25 We need to keep in mind that commonly the

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1 basal epithelium is not included, and in women  
2 .cervical sample is certainly the most commonly used  
3 and most appropriate, and the appropriate sample for  
4 similar screening in males is not at all clear.

5 Now, estimates of HPV associated disease  
6 in the United States have been made. Approximately  
7 one percent of the population has had genital warts.  
8 They are colposcopic or subclinical changes  
9 anticipated to be found in another approximately four  
10 percent.

11 There is approximately another ten percent  
12 that would have DNA positivity with no lesions, and if  
13 you include antibody positivity, which includes those  
14 that have a history of infection, you get over to 60  
15 percent.

16 And given that HPV antibody methods are  
17 not positive in all of those that have been infected,  
18 you can estimate that over 75 percent of the  
19 population in the United States has been exposed to  
20 HPV. And so that gets us back to the situation that  
21 HPV indeed is a very common and to be expected  
22 exposure with sexual activity.

23 Again, genital HPV is acquired around the  
24 time of sexual debut. The usual natural history is  
25 that infection is transient and is not associated with

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1 symptoms, and it is well recognized that persistent  
2 infection is more likely to be associated with  
3 potential for neoplastic progression.

4           There have been already reviewed for you  
5 very elegant and consistent epidemiologic associations  
6 of HPV with the cervical cancer precursor lesions.  
7 There are very plausible biologic mechanisms for HPV  
8 oncogenesis, and it just needs to be reemphasized that  
9 HPV oncogenesis is a really rare event with a long  
10 interval between infection and cancer, and infection  
11 alone is insufficient to cause the cancer, and  
12 additional factors are needed to be present in order  
13 for neoplasia to occur.

14           Now, there are many questions about HPV  
15 infection. One of them that will come up with  
16 increasing numbers of people being tested for HPV is  
17 is HPV eliminated. Will a person ever be cured of  
18 HPV?

19           HPV clearing is certainly monitored by DNA  
20 detection in cytology samples, and negative results  
21 indicate that the virus is shed below the limits of  
22 detection. But often the basal epithelium is not  
23 sampled, and HPV in some instances has been detected  
24 in histologically normal margins surrounding growth  
25 lesions.

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1                   We really don't know what the potential  
2                   for HPV persistence is in the host.

3                   There is evidence that duration of HPV  
4                   infection is generally of relatively short time frame  
5                   with those oncogenic types predominantly studied are  
6                   the HPV 16 and 18, having a longer degree of  
7                   persistence than the lowest types.

8                   However, a persistent infection does not  
9                   have a consensus on what the definition is, and in  
10                  order to really identify a persistent infection, you  
11                  would have to actually identify the same HPV type on  
12                  more than one occasion. If you have a time interval  
13                  between three to six months, which is what's most  
14                  often used, longer intervals, you can't exclude the  
15                  potential for reinfection, and consistent detection on  
16                  each occasion could perhaps have a different meaning  
17                  than intermittent detection, and this is really  
18                  unknown.

19                  Latent infection is kind of the formal  
20                  definition of it, would be the presence of HPV DNA and  
21                  the absence of a virion detection or virion  
22                  production, and that's certainly not practical because  
23                  we don't have any good ways of detecting the virions.

24                  So practically, the practical definition  
25                  is detection of HPV DNA in the absence of any

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1        identifiable lesion, and this is a situation of HPV  
2        DNA positive normal cytology, and this has been  
3        equated with occult infection.

4                Now, as I mentioned, the HPV testing is  
5        complicated by the nature of the virus and the fact  
6        that it's a family of virus. These multiple HPV types  
7        complicate any kind of assays.

8                The sensitivity and the pipe specificity  
9        varies with different assays, and inter-assay  
10       comparisons are difficult, if not impossible, and that  
11       is hybrid capture results are difficult to compare  
12       with any one other specific test.

13               And then just to review and reiterate what  
14       Digene has already told you, the HPV hybrid capture is  
15       the current FDA approved format. In 1999, it was  
16       transferred to the micro titer format. It is a liquid  
17       hybridization technique, and it uses chemiluminescent  
18       detection.

19               The signal is semi-quantitative, and this  
20       has been addressed indirectly by several questions at  
21       the end of Digene's presentation, but there is no  
22       control for the amount of input DNA. The RNA probes  
23       react with the DNA targets, and the RNA DNA hybrids  
24       are both captured and detected with monoclonal  
25       antibody to the RNA DNA hybrid.

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1           The test mix includes high risk versus low  
2 risk probe nicks (phonetic). The results, therefore,  
3 are not type specific.

4           Studies to date have shown very good  
5 interlaboratory comparisons particularly when  
6 laboratories have been well trained in the actual  
7 performance of the assay.

8           The hybrid capture assay is designed to  
9 work with exfoliated cervical sample, and there's a  
10 recommended collection kit that includes both the  
11 brush and the sample transport media, and calculating  
12 in the yield of cells that's involved, approximately  
13 five percent of the total specimen is assayed for each  
14 of the probe groups.

15           Now, by comparison, HPV PCR assays target  
16 a very small portion of the genome. The hybrid  
17 capture assays actually include probes to the majority  
18 of the HPV genome.

19           This allows testing of samples with poor  
20 quality DNA. It does have the potential that small  
21 changes in the virus, such as variance or integration  
22 of the virus may give false negative results. The  
23 amount of DNA, in other words, the portion of the  
24 sample that's actually assayed in PCR assay will vary,  
25 and it's usually less than five percent of the sample

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1       that's put into the hybrid capture reaction.

2               This will limit the number of cells  
3 actually sampled by a PCR test, and that's one of the  
4 reasons why standardization of PCR results is  
5 difficult to achieve.

6               PCR assays can be type specific, and these  
7 generally target the oncogenic region of the virus,  
8 but those that are most widely used in epidemiologic  
9 studies are consensus assays that target the L1  
10 region.

11              This then also requires additional testing  
12 to determine the specific type.

13              Now, the question of viral load and  
14 quantitation, whether this could potentially improve  
15 the specificity of the HPV as sort of a molecular  
16 marker for neoplasia has some problems, and part of  
17 this is because the viral load is difficult to  
18 estimate because of the uneven tissue distribution of  
19 the virus within the lesion and variations in the  
20 sample.

21              At the bare minimum, it requires some  
22 measure of the number of cells in the assay, that is,  
23 some sort of a denominator, and quantitative PCR  
24 assays are usually type specific and so you're limited  
25 in what you're actually quantitating.

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1                   And last but not least, just in the spirit  
2 of sort of giving everybody information on what is  
3 possible, HPV in situ hybridization is a tool that has  
4 been used in some studies. It's really the only  
5 approach that allows direct visualization of the virus  
6 in a morphologic context, but the results are  
7 extremely technique dependent and it has a very large  
8 learning curve in order to achieve sensitivity and  
9 specificity that would be acceptable.

10                   Now, this review was given in the spirit  
11 of just trying to put everything in the context of  
12 what HPV is, not just a single entity.

13                   CHAIRMAN WILSON: Thank you, Dr. Unger.

14                   Does anyone on the panel have a question  
15 for Dr. Unger?

16                   (No response.)

17                   CHAIRMAN WILSON: No? Okay. Thank you.

18                   All right. At this point we'd like to  
19 move on to the FDA presentation, and again I'd like to  
20 remind Panel members that they should hold questions  
21 until both of the presentations have been completed.

22                   I'd also like to remind the audience that  
23 only the panel can ask questions of the speakers.

24                   The first speaker today is Mr. Thomas  
25 Simms, who is a Senior Review Scientist with the

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1 Virology Branch.

2 MR. SIMMS: Good morning. I am Tom Simms.  
3 I am a reviewer in the Virology Branch.

4 And as you all know we're here to discuss  
5 a new indication for use for the Digene hybrid capture  
6 assay. What I'd like to do today is just briefly go  
7 over the new indications for use and discuss FDA  
8 issues with the submitted study populations; issues  
9 where the device is used in the various studies; a  
10 summary of these issues; and DR. Kondratovich will  
11 present a statistical overview, FDA's statistical  
12 overview.

13 The indication for use that's under review  
14 today is actually, I believe, in two parts. The first  
15 part, and I've highlighted what I believe are  
16 pertinent parts of the indication for use; that is is  
17 a general population screening test; and that in women  
18 with a concurrent normal PAP smear and a negative IV  
19 capture II HPV result, the probability of detecting  
20 evidence of high grade cervical disease upon  
21 colposcopy is reduced relative to the normal PAP  
22 result alone.

23 The second part reiterates that it is a  
24 screening test, screening for women in the general  
25 population, and that it will offer a single time point

1 assessment of the risk of having developed cervical  
2 disease, and the probability of detecting evidence of  
3 high grade disease upon colposcopy.

4 And since we are talking about a screening  
5 test today, perhaps it's a good time to review  
6 definitions for screening tests, and in the recent  
7 article that the New England Journal of Medicine, Lee  
8 and Brennan gave what I consider to be very good  
9 definitions, and they stated the screening tests  
10 should have a high sensitivity for detecting  
11 previously undiagnosed disease, and earlier detection  
12 should lead to changes in management that improve  
13 patient outcomes.

14 They go further to state that screening  
15 tests should also have low false positive rates so  
16 that large numbers of healthy people are not unduly  
17 alarmed or subjected to unnecessary tests and  
18 procedures and follow-up.

19 And perhaps this is a good time to review  
20 what the FDA review task is and what we try to do is  
21 evaluate assay effectiveness in the specific  
22 population claimed for assay performance  
23 characteristics and appropriate assay result  
24 interpretation, and this is based on the information  
25 that is submitted to us for review.

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1                   And as we've heard previously today, the  
2                   information that was submitted to us is from eight  
3                   studies. Two of these were performed in the United  
4                   States. Six are from non-U.S. sites, and information  
5                   from four of the studies have been published.

6                   The studies were not originally designed  
7                   to evaluate Digene's proposed indication for use. Our  
8                   established performance characteristics are the  
9                   resulting interpretation, and Digene and the FDA do  
10                  agree that the information is non-poolable across the  
11                  sites.

12                 And I'd like to make a comment that none  
13                 of the studies furnish as a longitudinal component to  
14                 assess the temporal relationship of HPV positivity to  
15                 disease detection, and all of our comments pertaining  
16                 these studies are in the context of the information  
17                 being used by Digene to support a specific indication  
18                 for use, and the comments are not reflective on how  
19                 the studies were conducted or are they meant to  
20                 evaluate the data for the original study hypothesis.

21                 For concerns with the study population  
22                 related issues, there's the issue of the study  
23                 populations perhaps not being consistent with U.S.  
24                 populations in that we have different high risk HPV  
25                 DNA prevalence across some of the populations.

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